ANIMAL STUDIES OF A. H. ROFFO, 1936-1943:

Roffo (1936, 1937a) painted destructive distillates of Kentucky tobacco daily on the inner side of rabbits' ears. The watery fraction that boiled in the range 0°- 120° C. and that contained largely nitrogen bases produced no tumors during a period of ten months. The tarry fraction that boiled in the range 120° - 350° C. produced papillomas in many animals within a period of seven months following the initiation of painting. These growths assumed the histologic character of squamous epitheliomas within a period of nine months following the initiation of painting. Of twenty animals painted with this tarry fraction, four died within the first month. The residual tar that boiled above 350° C. also produced carcinomas but with a lower incidence than the 120-350° fraction did. Spectrographic investigation of the tar fractions by Roffo (1937b) failed to demonstrate the presence of 1,2-benzanthracene, but did show the presence of other fused aromatic nuclei.

Roffo (1938) obtained similiar results with Egyptian and Turkish tobaccos. In subsequent publications (1939a, 1939b, 1939e) he reported studies with nine varieties of tobacco involving the painting the ears of rabbits every second day with a destructive distillate of tobacco that boiled in the range 120° - 350° C. The first papilloma occurred at at 26 days and many tumors developed between the 40th and 50th days. The tars from each variety of tobacco produced tumors in most of the experimental animals. From the statements of Roffo, it must be inferred that many of these tumors were papillomas, but he stated specifically that ten rabbits which were painted with the tar from Egyptian tobacco for a

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period of eight to fourteen months developed squamous cell carcinomas.

Roffo (1939a, 1939b, 1939d) recorded detailed spectroscopic studies of the destructive distillates of tobacco heated at 380° C. He obtained absorption bands suggestive of benzpyrene. In a further paper, Roffo (1939e) reported the distillation of a product from tobacco tar having the full fluorescent spectra of benzpyrene. This product was strongly carcinogenic for rabbits as shown by the formation of tumors that developed like carcinomas as judged by their extensive invasive and destructive growth. The animals usually died within one to two years after the start of the experiment. The initial lesions appeared earlier than when whole tobacco tar was used. Roffo concluded that the carcinogenic action of whole tobacco tar is due to its benzpyrene content.

Roffo (1939d) used tar from nine different strains of tobacco and obtained a carcinogenic effect on rabbit ears amounting in some strains to as much as 100 percent. The action was reported to be strongest with Turkish, Egyptian and Kentucky tobaccos and with chewing tobaccos. It was less marked in varieties from Havana, Italy, Corrientes, Paraguay, Germany and Salta(?). However with these latter varieties, carcinomatous growth was recorded in more than fifty percent of the animals. Roffo stated that the carcinogenic effects observed were a property of tar, not of nicotine, and that tobacco tar behaves like coal tar. The tumors observed by this worker developed in the same manner

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in all cases. Hyperkeratoses and papillomas developed first and after nine to ten months these were converted into pavement cell carcinomas (infiltrative malpighian epitheliomas). Roffo observed that only 100 to 150 grams of tobacco tar were required to produce these carcinogenic effects on the inner ear of the rabbit when painting was carried on every second day. He noted that a moderate human smoker of tobacco produces about 840 grams of tar in a year.

Roffo (1939d) described the composition of the fractions obtained by the destructive distallation of tobacco leaves. By his procudure three fraction were obtained: (1) On heating at 100-120°, there distilled an aqueous liquid, dark yellow in color and strongly alkaline, and containing carbon monoxide and dioxide, ammonia, methyl alcohol, acetates, pyridine, methylpyrolidine, aldehydes, furfural and empyreumatic substances; (2) On raising the temperature to 350° for two hours there was was obtained solid, alkaline resinous material containing carbon monoxide and dioxide, ammonium carbonate, succinates, fumarates, citrates, uncharacterized phenols, pyrrole and its derivatives, pyridine and methylpyrrolidine, derivatives of chlorophyll, stable hydrocarbons, phenanthrene, anthracene and benzpyrene, etc. (3) A non-volatile residue remained containing salts of potassium and sodium including nitrates, carbonates, bicarbonates and chlorides, carbon, and fused-ring hydrocarbons. Roffo reported that the amount of tar obtained from various tobaccos varied from 41 to 110 grams per kilogram of tobacco. The second fraction produced carcinomatous growth in 98 percent of the rabbits, the third fraction in about 70 percent, while the first, low boiling fraction had no activity. The evolution of these tumors was small in respects similar to that induced by coal tars

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Roffo (1939f, 1939h) reported that tar ~~from tobacco smoke~~ produced by ~~tumors when applied to the rabbit ear.~~ Bubbling ~~the~~ tobacco smoke through water, as in a narghile pipe, or filtering the smoke through cotton, removed ~~an appreciable~~ a portion but not all of the carcinogenic ~~substances.~~ activity. The tar, extracted from the water or from the cotton filter, was painted on rabbits' ears every other day. Under these circumstances, the first papilloma was seen at 49 days and 8 rabbits developed tumors by ~~222~~ the 290th day. At twelve months, each rabbit had from six to thirteen tumors, some of which were described as squamous cell carcinomas.

Roffo and Luchetta in 1940 ~~reported~~ published a study describing the hematologic changes of rabbits with ~~cancer~~ tumors produced by tobacco tar. They reported that painting rabbits with tar obtained from the pyrogenic distillation of dry tobacco leaves did produce ~~true cancer.~~ carcinomas. ~~All hematic elements underwent~~ hematologic were observed in the ~~More~~ erythrocytes, ~~which presented modification in 3 distinct stages.~~ more or less pronounced changes, particularly ~~the~~

Roffo (1940) reviewed his earlier work and ~~reviewed~~ stated the conclusion that neoplastic proliferations produced by tobacco tar in animals are more malignant than those induced by coal tar. Furthermore, tars extracted from various/tobacco varieties of showed similiar carcinogenic characteristics. Roffo (1941a) again reviewed his earlier work with the addition of a small amount of additional animal experiments. When the skin of twenty rabbits was painted with the fraction obtained by the dry distillation of tobacco at a temperature of about 100° C., no lesions developed. When a similar number of rabbits were painted

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with the fraction distilled at 120°-135° C., two papillomas were produced which later developed into carcinomas. From this distillate Roffo reported the isolation of benzpyrene which proved highly carcinogenic in animals.

Roffo (1941b) ~~administered orally~~ 0.15 cc. of tobacco tar daily to 57 rats per 120 grams of body weight. This dosage of tar was relatively non-toxic as was proven by the longevity of the animals, some of them reaching more than two years of age. Gastric lesions developed in about fifty percent of the animals. Roffo stressed that it was essentially the glandular zone of the rats' stomach which suffered most from the action of tobacco tar, although some hyperplastic papillomatous lesions were also found in the squamous zone and even in the epithelial border. Development of Cancer ~~Cancerization of these~~ gastric lesions was reported to take place only after a prolonged period of feeding. The first signs of the malignant process often appeared one year after the start of the experiment. However, fifty percent of the animals a variety of gastric lesions, developed after a period varying from five to thirty months.

Roffo (1942a) reported that tumors induced by tobacco tar on the ears of 1,000 rabbits were carcinomata. However, in one animal a massive tumor of the fusocellular sarcoma type had developed. This had appeared on the 49th day following the initiation of painting. Carcinomas were also evolved. The animal died on the 360th day, the sarcoma having reached three centimeters in diameter. Roffo concluded that tobacco tar has a carcinogenic effect upon the basic tissues of the organism, namely by inducing carcinomata in the epithelial tissues and sarcomas in the connective tissues.

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Roffo (1942b) ~~extracted the~~ by extracting tobacco [redacted] with organic solvents such as alcohol, chloroform, acetone, petroleum ether, paraffin, ~~and~~ or benzine. [redacted] was able to eliminate substances which generate carcinogenic hydrocarbons ~~with~~ on combustion or destructive distillation of the tobacco. These substances were found especially to be among the phytosterols. Phytosterols were stated to constitute approximately 0.53% percent of the dry substances in black tobacco, and 0.78% percent in the golden variety. These percentages are large as compared with extracts from food plants, for ~~instance~~ example the potato, with 0.15% percent, cabbage with 0.12% percent, oats with 0.20% percent, and squash with 0.15% percent. Experiments ~~with tar extracted in the manner described showed that it~~ (In animal) was only mildly carcinogenic as compared with ~~experiments in which~~ whole tar ~~was used~~. The tumors in the experimental animals painted with extracted tar were reported to be ~~were, according to Roffo,~~ anatomical and histological by keratosic papillomata which failed to develop into cancer. ~~The experimental~~ Animals, treated with the extracted tar, lived longer than those treated with whole tar. On the basis of this work, Roffo suggested that tobacco that has been extracted to remove a portion of this tar content would provide a [redacted] less irritating smoke.

[redacted]

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Roffo (1943a) injected tobacco tar directly into the lung parenchyma of an animal (rabbit?) and reported that at the end of eight months the animal was killed and autopsied four small tumors were observed at the site of the injection, all having the character of squamous cell carcinomas with horny globules.

Roffo (1943b) reported the appearance of distant metastases by painting the ears of a single rabbit with tar from the destructive distillation of tobacco for a period of 382 days.

A. E. Roffo, Jr. (1938) reported a spectrographic study of blood from rabbits and from human smokers. In one set of control animals carbon monoxide was determined in known dilutions of hemoglobin. To one experimental group of animals of equal age and weight was administered tobacco smoke intranasally each day for a period of 2 1/2 months. Spectrographic examination of the blood for carbon monoxide at intervals of 1 to 84 days showed that it was not present in the controls, while in those inhaling tobacco smoke the carbon monoxide was present in direct proportion to the amounts of smoke inhaled. This increase varied from 0.1022 to 0.3247 cubic centimeters per 100 cubic centimeters of blood during the extremes of the smoking period. In further work, A. E. Roffo, Jr. (1938, 1941) extended these findings to human subjects some of whom had cancer some smokers and some non-smokers; some urban dwellers and some living in

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of persons exposed to either tobacco smoke or city air. This worker felt that although the carbon monoxide blood levels observed were far below the toxic dose, the slow and chronic asphyxia created might possibly prepare the ground for cancer production or stimulate the growth of existing carcinomata.

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STUDIES OF TOBACCO AS A NEOPLASTIC AGENT IN ANIMALS, 1940-1950.

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~~might be of significance since it might prepare the ground for carcinogenesis and also enhance the growth of existing carcinomata.~~

~~EXPERIMENTAL STUDIES ON TOBACCO AS A NEOPLASTIC AGENT~~ IN ANIMALS 1940-1950

Sugiura, in 1940, heated leaf tobacco in an iron still at from 100° C. to 500° C., then at from 500° to 900° C., collecting the products of each distillation. Subcutaneous or ~~intermuscular~~ intra injection of 0.1 cc. of either distillate killed young adult rats or mice within one hour with violent convulsions being observed. ~~Groups of~~ Mice were painted twice weekly with the distillates. With the 500° to 900° C. distillate, one case of squamous cell carcinoma developed ~~in a series~~ out of 168 surviving Bragg albino mice at the site of painting. This carcinoma appeared in a mouse ~~mice~~ painted for 315 days, the normal life span of this strain of mice being 90 to 500 days. Using ~~the~~ an oily mixture of both distillates, this worker painted the skin of C57 black mice and of dba mice as well as the ears of Wistar rats and of rabbits of common stock with tobacco tar for periods up to 65 weeks. In no ~~animal~~ one of these animal strains and species was a cancerous change observed. The proliferation capacity of mouse sarcoma 180 and Flexner-Joblin rat sarcoma was unaffected by tobacco tar or by a pure nicotine solution brought to pH 74. ~~Sugiura~~ Sugiura concluded that tobacco tar can be only a very weak carcinogen if at all.

Flory in 1941 reviewed ~~a considerable amount of~~ the literature ~~described in detail above~~ and reported further studies on the production of tumors in animals under the influence of tobacco tars. Twelve rabbits were painted on the ears five times weekly with tar produced by the destructive distillation of tobacco at 350° to 700° C. (temperature electrically controlled). Between ~~six~~ 49 and 79 days all the rabbits developed tumors at the ~~sight~~ site of painting. The rabbits lived from 238 to over 660 days. Sixty-eight of the tumors were examined histologically and were reported to be papillomas; and ~~3~~ five were reported to be carcinomatoid tumors. No carcinomas were produced. ~~At 130° to 350° C.~~

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A destructive distillate tar (boiling range 130-350°) produced tumors in sixteen out of seventeen rabbits, but more slowly than the 350° to 700° C. tar. Forty of these tumors were papillomas and five carcinomatoid tumors. Twenty-four rabbits were painted with tar obtained by smoking tobacco in pipes. Tumors were produced in from 37 to 374 days in 22 out of the 24 rabbits. Seven animals lived over 640 days. Thirty-six tumors from this source examined histologically were papillomas and two were carcinomatoid tumors. Again, no carcinomas were produced. The tar obtained in either manner produced tumors less readily when painted on mice, but the ~~denicotined~~ denicotinized 350° ~~to~~ — 700° C. distillate produced eight papillomas and one squamous cell carcinoma which ~~arose~~ developed at 8.5 months when 14 mice were alive out of an original series of 46. Denicotinized pipe tar in mice produced two papillomas and one squamous cell carcinoma which arose at 17 months when 22 mice were alive out of an original series of 60 mice. Among 2,000 mice of this strain, no spontaneous skin tumors had been observed in a two year period. Flory also discussed in detail the classification of tar tumors. Following the terminology of Rous and Kidd (1939, 1940) he divides tar induced rabbit tumors into four groups: common papillomas, frill horns, carcinomatoids (or carcinoids), ~~carcinoids~~ and carcinomas. By ~~carcinoids~~ carcinomatoids are meant tumors which have the morphology of squamous cell carcinomas, yet vanish or assume a benign form when the treatment is discontinued. ~~when tar is left off. These tumors are also referred to by Rous and Kidd and by Flory as carcinomatoid.~~ All these workers are in agreement that extreme anaplasia of a locally invasive nature may raise the question of malignancy but not establish it beyond question. The only true criterion for a carcinoma of the ear of a rabbit is a metastasis to a lymph node or other distant site, or the existence of a tumor that is transplantable. Ulceration, local destruction of the ear and local lymphatic vessels may

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all occur in carcinomatoid tumors. The original article of Flory should be consulted for full histological details. It should be pointed out that Flory questioned many of the earlier observations concerning the carcinogenicity of coal tars holding that many reported carcinomas may well have been merely carcinomatoid tumors.

Flory concluded that by painting ~~the~~ destructive distillates of tobacco and pipe tars on rabbits proved carcinomas have never been produced, but only papillomas and carcinomatoid tumors. "Papillomatous growths", he stated, "~~are~~ are produced by known carcinogenic agents before the true carcinomas appear, but these benign tumors have not been proved to be any indication of the carcinogenic activity of the substance producing them." As two squamous cell carcinomas were developed by painting mice of the same stock with tobacco tars or destructive distillates, Flory concluded that both may have a low ~~but definite~~ carcinogenic activity.

Grace, in a series of papers (1943a, 1943b, 1944), attempted to coordinate any possible relationship between the deposition of tar in the bronchial vessels after cigarette smoking and lung cancer. He cited at length some of the salient points of Roffo's work, but presents no additional animal work. ~~His clinical observations are discussed at another point in this review.~~

Lorenz and co-workers in 1943 reported a study of the effects of breathing cigarette ~~tobacco~~ smoke on strain A mice. An automatic tobacco [redacted]machine was used to expose mice for several hours daily to

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

tobacco smoke. Ninety-seven control and the same number of strain A ~~experimental~~ mice ~~(strain A)~~ of both sexes were kept in a chamber through which the smoke passed several hours daily maximally to 693 hours per mouse, for 25 to 250 days. The average smoke content of the air in the chamber was one milligram per liter, and the amount of tar deposited in the respiratory passages of any one mouse during the entire experimental period was calculated to be approximately 0.5 milligrams. Lorenz and his co-workers reported that no increase in tumors was induced by the tobacco tar, the average number of spontaneous pulmonary tumors was the same in both the experimental and control mice. On autopsy, pigmented foci were observed in the lungs of all mice exposed to tobacco smoke for more than three months, probably indicated areas of deposited tar. A few experimental animals showed inflammatory lesions of the stomach and duodenum.

Additional apparently unpublished work of the National Cancer Institute has been recently cited by Maisel (1950) and in a news release (Anonymous, 1950g). Tobacco tar was injected under the skin of one group of mice, it was suspended in the drinking water of another group, and in a further group, a tobacco tar suspension was injected repeatedly into the blood stream so that tar particles would be lodged in the lungs, and all of the mice so treated remained as tumor-free as their control litter mates.

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Campbell (1944) ~~in experiments of tobacco smoke inhalation by mice~~ reported that neither alcohol in the ~~smoking~~ drinking water in moderate amounts nor inhalation of tobacco smoke had any effect in mice upon the action of inhaled anthracite coal dust on the fibrous tissue of the lung.

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Haag and co-workers (1946) exposed a group of sixteen white rats (twelve females, four males) from weaning age to cigarette smoke fourteen times daily at half-hour intervals for their entire life span. The smoke was generated by a multiple cigarette smoking machine constructed to simulate human smoking. One control group of rats was kept in cages in an animal room, and a second group was kept like the experimental animals except for smoking. The life span of the smoking group was 642 days, of the smoke controls 544 days and of the cage controls 631 days. Necropsy observations demonstrated no lesions peculiar to any of the three groups.

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Neal, McDougle and Sweets (1949) implanted into the orbital sinus of four domestic fowls "the residue material accumulated in the bowl of a tobacco pipe". After 771 days, no neoplasms were produced at the site of implantation, and in a similar experiment, no neoplasms were produced by implantation of 1,2,5,6-dibenzanthracene.

Kemler and Graham (1950) attempted to ascertain whether the sex preference of lung cancer was real or only apparent. The technique of Greene was employed involving the transplantation of human lung cancer tissue into the anterior chamber of the eyes of female or male guinea pigs. The female animals could be made more 'female' by previous administration of female hormones, and similarly, the male animals were made more 'male' by administration of male hormones. In this technique, where a true sex difference in a given cancer is present, the percent success in transplantation of it on to the eye of the two sexes will vary. However, these workers found with human lung cancer no significant difference in the number of takes in the female and male animals. They concluded that this finding suggests that no true sex difference may exist in lung cancer with regard to susceptibility.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

STUDIES ON TOBACCO AS A POSSIBLE NEOPLASTIC AGENT

(adapted in part from Flory, 1941)

(See footnote for explanation of abbreviations)

Author & Yr. of Publication	Tobacco[1] Form Used	Mode of[2] Adminstr.	Animal[3] Species	Dura[4]-tion	Results[5]
Brosch, 1900	Tob. juice	Pa., sk.	G.p, rab.	?	Prolif.
Zborowski, 1908	Cig. smoke	Inhal.	rab.	57-180 D	2 died after 57 & 66 D, 2 killed at 129 & 180 D; no atypical growth
Stocker & Wacker, 1910	Pyridine fr. tob. smoke	Pa., ears	Rab.	?	Epithelial growth
Wacker & Schmincke, 1911, 1912	Tob. pipe tars	Inject., ears	Rab.	21 D	Prolif.
Hoffman et al., 1923a	Tob. tar, denicot.	Pa., sk.	Mice	80 D(?)	Hair loss, No prolif.
Hoffman et al., 1923b	" "	Pa., sk.	Fowls	?	Hyperkeratosis
Bergerhoff, 1923 (?)	Tob. tar denicot.	Pa. sk.(?)	Mice	80 D	No atypical growth
Helwig, 1928	Tob. pipe tar	Inject.	Rab.	4 M	Prolif.
" "	Nic.-free extr. of pipe tar	Pa., sk.	Mice	8-10 M	Benign Ulcers
" "	400-500°C. destr. dist. of tob.	Pa., sk.	Mice	8-10 M	Benign ulcers
Leitch, cited by Helwig, 1928	Chloroform extr. of tob. tar	Pa.	?	?	Ulceration, but no prolif.
Mertens, 1930,	Cig. smoke	Inhal.	Mice	>149 D	In 125 mice, 1 adeno-carcinoma, no metastasis
Mertens, 1941	Cig. smoke & coal tar Pa. of skin	Inhal.	Mice	up to 475 D.	No pulmonary growths
Roffo, 1930a, 1930b, 1931a	Tob. smoke	Blow on lip	Rab.	?	Occasional oral leukoplakia
	Conc. tob. smoke	Pa., ear	Rab.	6-8 M	Papillary ca. on ear
Roffo, 1931b	Nicotine	Inject.	Rab.	8-12 M	No lesions

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

Author & Yr. of Publication	Tobacco[1] Form Used	Mode of[2] Adminstr.	Animal[3] Species	Dura[4] -tion	Results[5]
Chikamatsu, 1931	Tob. tars	Pa., ears	Rab	225 D	Cancroid of ear
" "	" "	Pa., ski	Mice	?	No results recorded
Cooper et al., 1932	Tob. pipe tars extr. & destr. dist.	Pa., sk.	Mice	23 M	In 50 mice, 1 ca.
Roffo, 1931b, 1932	Jet of tob. smoke	Imping., ear	Rab.	3 Y	1 ca. in 10 rab., metastases
Roffo, 1932	Pill of tob. tar	Implant., bladder	Rats	8-20M	Neoplastic-like lesions
Moratti, 1932	Cigars	Implant, gallbladder	Dogs	?	Chronic Inflammation
" "	Nicotine	Inject., breast	Dogs	?	Chronic Inflammation
Bogen & Loomis, 1932	Tar denicot. fr. destr. dist. of tob.	Pa., sk.	Rab. & Mice	6-12 M	No effect
McNally, 1932	Tob. tar.	Pa., sk.	Rats	110 D	Too toxic.
" "	H_2O sol. of tob. smoke	Spray mouth	Rats	97 D	No effect.
Lu, 1934a, 1934b	Tar from tob. comb. 1 ear & coal tar other	Pa., ears	Rab.	148-182 D	3 of 8 rab. develop ca. on tob. ear, but ca. on coal tar ear earlier
" " "	H_2O sol. of tob. smoke	Pa., ears	Rab.	?	No effect
Schürch & Winterstein, 1936a	Tar denicot. fr. cigar smoke alone or with thermal injury	Pa., sk.	Mice	258-635D	No tumors
" "	Distillates of above tar	Pa., sk.	Mice	60-480 D	No tumors
" "	Coal tar to 1 ear until warts, amputated, then cigar smoke tar to other ear	Pa., ears	Rab.	918 D	Ca. in 1 rab. at 344 D, warts in 6 at 918 D.
Schürch & Winterstein, 1937	As above with coal tar then tob. tar	Pa., ears	Rab.	48 M	Ca. in 1 rab., Warts in 2

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Author & Yr. of Publication	Tobacco[1] Form used	Mode of[2] Administr.	Animal[3] Species	Duration[4]	Results
Campbell, 1934, 1936	cig. smoke	inhal.	mice	-	No signif. diff in ca. response of exptl mice and controls
Campbell, 1934,'36,'39	cig. smoke tar	Pa., sk.	Mice	16 M	1 ca. (?)
Taki (See Kinoshita, 1937)	tob. pipe tar denicot.	Pa.	Mice	130 D	2 ca., & 3 papillomas
Roffo, 1936, 1937	tars from destruct. dist. of tob.	Pa.	Rab.	9 M	Squamous epitheliomas
Roffo, 1938	as above	Pa.,ears	Rab.	8-14 M	Squamous cell ca. in 10 rab.
Roffo, 1939e	fused-ring hydrocarbon from tars as above	Pa., ears	Rab.	?	Initial lesions earlier than with whole tar
Roffo, 1938f,1939h	tars from tob. H_2O sol. of tob. smoke, or from filtering same thru cotton	Pa., ears	Rab.	12 M	Squamous cell ca. in 8 rab.
Roffo, 1941b	tars from dist. of tob.	fed	Rats	1-2 Y	gastric ca. and other lesions
Roffo, 1942a	as above	Pa., ears	Rab.	1 Y	1 massive fusocellular sarcoma of ear in 1,000 rab. and many ca.
Roffo, 1943a	as above	Injected lung	Rat	8 M	4 tumors at inject site
Roffo, 1943b	as above	Pa., ears	Rab.	382D	1 ca. of ear with distant metastases
Sugiura, 1940	as above 500-900° dist.	Pa., skin	Mice	315D	1 ca. in 168 mice
[redacted]	as above mix. of 100-500° and 500-900° fractions	Pa., skin or ears	Mice, rats, & rab.	up to 65 W	no effects

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

Author & Yr. of Publication	Tobacco[1] Form used	Mode of Adminstr.	Animal Species	Dura -tion	Results
Flory, 1941	Destruct. dist. of tob. 350-700° fraction	Pa., ears	Rab.	238-650 D	In 10 rab., all develop carcinomatoid tumors & papillomas, but no ca.
	as above, 130-350° fraction	Pa., ears	Rab.	640 D	In 16 of 17 rab. papillomas & carcinomatoid tumors but develop more slowly than with higher fraction; no ca.
	as above, denicot., 350-700° fraction	Pa., sk.	Mice	8.5 M	Of 46 mice, 14 alive at 8.5 M. Then 1 squamous cell ca. and 8 papillomas.
	Pipe tar, Denicot.	Pa., sk.	Mice	17 M	Of 60 mice, 22 alive at 17 M, then 2 papillomas & 1 squamous cell ca.
Lorenz, 1943	Tob. smoke	Inhal.	Mice	25-250 D	No signif. ca. response
Nat. Cancer Inst. (see Maisel, 1950; Anon., 1950g)	Tob. tar	1) Inject skin; 2) inject blood stream; 3) in drinking H_2O	Mice	?	No signif. ca response
Haag et al., 1946	Tob. smoke	Inhal.	Rats	642 D	No ca. response.
Neal et al., 1949	Residue from tob. pipe	Implant., orbital sinus	Fowls	771 D	No neoplasms.

Abbreviations: 1) Cig. - cigarette; cond. - condensed; denicot. - denicotinized; destr. - destructive; dist. - distillation or distillate; extr. - extract(ed); fr. - from; mix. - mixture; nic. - nicotine; pa. - painting; tob. - tobacco.
2) Imping. - impingment; implant. - implantation; inhal. - inhalation; inject. - injection; pa. - painting; sk. - skin.
3) G. p. - guinea pig; rab. - rabbit.
4) D - day; M - month; Y - year.
5) Ca. - carcinoma (or carcinogenic when used as adjective); D - day; diff. - difference; M - month; prolif. - proliferation; rab. - rabbit; tob. - tobacco; signif. - significant or significance.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

CRITIQUE OF STUDIES ON TOBACCO AS A NEOPLASTIC AGENT IN ANIMALS.

~~CRITIQUE OF ANIMAL STUDIES ON TOBACCO AS A NEOPLASTIC AGENT.~~

Many of the studies alleging the production of malignant neoplasms in animals by tobacco tars can be criticized adversely.

According to ~~Following~~ the work of Flory (1941) discussed above, much of the earlier work can be questioned on histological grounds. It is clear that ~~xxxx~~ prior to the restudy of the histological classifications after Yamagiwa and Ichikawa (1918) by Rous and Kidd ~~(1939, 1940~~ (1939, 1940, 1941) may have been many skin neoplasms ~~xxxx~~ imperfectly classified. Reported carcinomas of earlier workers may well have been carcinomatoid tumors only and not truly malignant. A large amount of experimental ~~xxxxx~~ work suggests that it is difficult to induce cancer in rabbits by tars from any source which fulfills all the criteria of malignancy. Even with so potent a carcinogenic agent as pure benzpyrene, the rate of carcinoma production in rabbits is extremely low (Brunschwig and co-workers, 1940; Schürch and Winterstein, 1935a, 1935b; Schürch, 1939). The statement of Flory (1941) in this connection is worthy of extended citation:

> "What then is the status of these carcinomatoid tumors? In this work with tobacco tars evidence does not indicate what the ultimate fate of these tumors would have been. Most of the tumors were identified only at autopsy, although some were seen very early in the painting period. It is of importance to note the absence of definite metastases in all 11 animals with carcinomatoid tumors. It was not proved that such tumors could produce distant metastases. In view of the work of Rous and Kidd it would seem likely that the invasive behavior of these tumors depended on the repeated application of an extrinsic stimulus rather than on an intrinsic capacity for unrestricted growth. There is no evidence that the production of these carcinomatoid tumors in rabbits is an indication of carcinogenic activity of the tobacco tar."

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It is interesting to note that apparently no worker has claimed the production of a carcinoma, by the application of combustion products of tobacco, that proved capable of transplantation - a critical test of true malignancy. And only Roffo (1942a, 1943b) has emphasized the production of neoplastic growth accompanied by metastasis to distant sites - a further test of true malignancy.

Flory (1941) commented directly regarding the work of ~~xxx~~ Roffo that some of the tumors seen by the latter and called carcinomas seem to be only carcinomatoid in character. The histological findings of Roffo in other animal work relating to the effect of cholesterol on tumor production has been criticized severely by Klein and Palmer (1941), by Cook and Kennaway (1940), by Kirby (1943, 1944, 1945) and by Poulsen (1949) and some of these workers have questioned the accuracy of Roffo's chemical and spectral identification of carcinogens in substances heated to high temperature. Recently Waller (1949) in an abstract of work apparently in progress on the benzpyrene content of air, dusts, soots, etc. has stated that no evidence has been found as yet of any production of benzpyrene in the combustion of tobacco.

A further valid criticism of some of Roffo's experiments and those of various other workers is that experiments involving tobacco tars produced by the destructive distillation of tobacco are unrealistic with regard to the smoking process. Temperatures employed in many dry distillations were at or beyond the extreme temperature range seen in the smoking process and the exposure of the tobacco to these temperatures ~~in the~~

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during the distillation is a matter of hours rather than seconds. Certain of the stills employed in such distillations involve the use of a free flame for heating, which makes local superheating possible and the attainment of local temperatures in excess of those usually observed in the smoking process. Furthermore, the absence of oxygen in the distillation process obviously alters the distribution and nature of the products obtained from those seen in the smoking process.

Some of the experimental work suffers the additional difficulty that the strains of the rats and mice employed were not always specified and ocasionally even such important data as the duration of the experiment, the number of animals employed, or the frequency of painting or other exposure are lacking. It is important to observe in this connection that Lynch (1933, 1935), Andervont (1938, 1940) and Greenstein (1947) have reported considerable variation in the susceptibility of various strains of rats and mice to the induction of tumors by tars and other carcinogenic agents.

It is also noteworthy that much of the animal work reported is somewhat unrealistic with regard to the smoking habits of man. The only extensive studies made with animals confined to an atmosphere of smoke for many months (Campbell, 1936; Mertens, 1930, 1941; Lorenz, 1943; Haag and co-workers (1946) have demonstrated no significant influence on the

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production of tumors of the smoking tract ~~of mice~~ of even inbred strains susceptible to pulmonary tumors. Lynch (1923, 1935) and Andervont (1938, 1940) have demonstrated that the influence of chemical agents on carcinogenesis varies markedly according to the route of administration. A given agent may induce a carcinogenic response when applied to the skin, but this provides no assurance that the same agent would induce lung neoplasms when administered in the gas or smoke phase.

It should be pointed out, however, that the inability to demonstrate a significant carcinogenic activity for the combustion products of tobacco ~~x~~ (or for any other material) in certain species the animal/does not constitute unequivocal proof that these products could not display such an activity in other species of animals or in man. The life span of the usual experimental animal is so short that chronic exposure to a very weak carcinogen or a strong one in very low concentration often fails to induce a significant carcinogenic response (see Stern and Willheim, 1943; Greenstein, 1947; and papers of Campbell).

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FINDINGS ON THE ALLEGED NEOPLASTIC RESPONSE OF ANIMALS TO TOBACCO AND ITS COMBUSTION PRODUCTS:

Extracts of tobacco and its combustion products have been applied to various parts of many species of animals for long periods in an attempt to ~~elicit~~ elicit a neoplastic response. Many of these experiments have yielded ~~equivocal~~ ambiguous data primarily because of faulty experimental methods and because of the employment of questionable criteria for determining the presence of true malignancy.

Only a small minority of the investigators working with tobacco tars or condensed whole smoke have reported any significant neoplastic response. In contrast, none of the studies in which animals were exposed to tobacco smoke over periods up to almost two years has reported ~~the production of cancerous growth.~~ any significant neoplastic response.

It might be argued that the experimental procedures employed were not sufficiently rigorous to ~~elicit~~ elicit the response. But, be this as it may, it must be emphasized that the animal studies reported to date have failed to ~~ascertain~~ demonstrate a ~~well-defined~~ carcinogenic activity for tobacco or its combustion products.

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CHAPTER VI

~~STUDIES OF~~ TOBACCO SMOKING IN THE ETIOLOGY
Lung Cancer
OF HUMAN BRONCHIOGENIC CARCINOMA

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A large number of papers ranging from undocumented assertions to extended statistical studies have alleged an association between the intensity and/or the duration of tobacco smoking and the incidence of lung cancer. In the present chapter these papers are considered in chronological order according to the year of publication. Papers alleging an association between the use of tobacco and cancer of the entire respiratory tract ("smoking tract") are also discussed. However, papers bearing only on the upper respiratory system (mouth, lip, larynx, etc) are not subject to review in the present survey.

STUDIES OF LUNG CANCER AND THE USE OF TOBACCO THROUGH 1934

Newman (1927) reported that among monks of orders that do not eat meat or smoke tobacco, only 4.9 to 5.9 percent die of carcinoma, while in Switzerland and in Denmark of people over 45 years of age about 20 percent die of cancer. Lickint (1933) commented on Newman's observation that vegetarianism alone has no marked effect on the incidence of cancer, and cited the observations of Milner that in India of 102 cancer cases seen, 61 had strictly vegetarian habits.

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The data of Hoffman (1925, 1927) from the San Francisco Cancer Surveys on the smoking habits of cancer patients were analyzed by Lombard and Doering (1928), and are presented in tabular form below:

CANCER SITES AND SMOKING
(Lombard & Doering, 1928) (Based on Hoffman, 1925, 1927)
(184 Cancer Cases)

	Cancer Sites Supposed to be Affected by Smoking	Cancer Sites not Supposed to be Affected by Smoking	Sarcoma	Total
Heavy smokers	34	100	11	145
Not heavy	1	34	4	39
Total	35	134	15	184
% of heavy smokers	97.2	74.6	73.3	78.8

Single case

As can be seen from the table, in this series of Hoffman 78.8 percent of all cancer patients were heavy smokers, while 97.2 percent of those patients with cancers of the sites supposed to be affected by smoking ("smoking traps") were heavy smokers. In a larger sample of 834 male patients (all cancers?) Hoffman reported (1927) 44.1 percent were heavy smokers. The term "heavy smoker" in these studies of Hoffman seems to have been only loosely defined

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Lombard and Doering (1928) collected data on certain habits, characteristics, and environmental factors of individuals with and without cancer by interview through visiting nurses organizations of Massachusetts. Each investigator collecting data on a cancer patient also filled out a similar record for a non-cancer patient of the same sex and of approximately the same age. A total of 217 cancer patients and a like number of controls were studied with regard to certain habits and characteristics appeared. Lombard and Doering, on the supposition that only cancer of certain sites ("smoking tract") should be affected by smoking, ~~and that sarcoma should not be influenced,~~ ~~thus~~ dividing all 45 of their cancer patients into smoking groups, ~~as follows:~~ total of but provided no information as to how these 45 were selected from the 217 cancer cases & their ~~tobacco~~ results are give below:

CANCER SITES AND SMOKING (Lombard and Doering, 1928)

	Sites Supposed to be Affected by Tobacco	Sites not Supposed to be Affected	Total
Heavy smokers	9	17	26
Not heavy smokers	8	21	29
Total	17	38	45
% of heavy smokers	52.8	44.8	47.3

Single space

Lombard and Doering in their paper do not define what is intended by "heavy smoker". ~~Analysis of~~ In their control group (similar age and sex distribution) ~~reported~~ 20 percent were heavy smokers, and in the total group of both cancer and control cases, 33.7 percent were heavy smokers. Lombard and Doering concluded that the difference of 27 percent

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between the cancer and control groups was significant and suggested that heavy smoking has some relation to cancer in general. Of the heavy smoking group constituted, 73.1 percent of the cancer group pipe smokers and 72.6 percent of the control group. These workers, in attempting to assign meaning to the percentage of heavy smokers in the cancer and control groups, observed that the percentage of heavy smokers in the general population is unreported. However, that 33.1 percent of 16,662 male policyholders of the Metropolitan Life Insurance Company were heavy smokers.

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Lickint (1929) observed that tobacco dust might on occasion be a causal factor in the development of cancers. He cited the earlier similar observations of Brinkmann (1914), Enger (1923), and Seyfarth (1924). Seyfarth (1924) had reported that in a period of six months out of eighteen cases of carcinoma of the lung observed, four were in cigar makers. Langbein (1923) reported in a series of 177 cases of carcinoma of the lung, 4 cases were cigar handlers. However none of these workers reported the proportion of workers in the tobacco industry among the population coming for examination.

Lickint (1929) cited the observation of Cheatle (1923) that cigarette smoke might be a factor in the development of skin cancer, and a statement by Bloch (1908) that tobacco workers have a high incidence of skin cancer. Lickint, however, reported that no further supporting evidence is contained in the earlier literature for these statements, and stressed that in smokers whose fingertips have been darkened by tobacco and its decomposition products for many years, no evidence of tumor formation has been reported in spite of the probable contact with the epidermis for many years.

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Lickint (1929) concluded that the smoking of tobacco may be one of the causal factors in the development of cancer of the lung. He went so far as to suggest that the occasional non-smoker who develops lung cancer may have had adequate such exposure to tobacco smoke in rooms filled with smoke.

Hoffman (1931) studied the smoking habits of 1,413 male cancer patients from major American cities. Of these patients, 20.8 percent were non-smokers, 33.6 percent were moderate smokers, and 45.6 percent were heavy smokers, of patients with cancer of the buccal cavity, 16.2 percent were non-smokers, 36.5 percent were moderate smokers, and 47.3 percent were heavy smokers. In other terms, of all cancer patients, 79.2 percent were smokers: in constrast, of buccal cancer patients, 83.8 percent smoked. For cancer of the stomach, the percentage of smokers was 79.2, and for cancer of the intestines, 66.3 percent. Hoffman also reported that of 27 patients with lung cancer, 18 or 67 percent were heavy smokers. He observed that such an analysis of smoking habits is not entirely trustworthy as many patients may smoke both a pipe and cigars, or cigars and cigarettes. These data are to be compared with those of Bogen (1929) and quoted by Hoffman (1931), to the effect that in a group of 630 men in an industrial population, 282 were non-smokers (44.8 percent), 269 were light smokers (42.7 percent), and 79 were heavy smokers (12.5 percent). In neither of these studies is the meaning ascribed to "heavy" and "light" smoking apparent. The terms "light" and "heavy" smoking seem not to have been precisely defined in either of these studies.

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Hoffman (1931) also recorded the smoking habits of 537 male patients with chronic diseases (heart disease, arteriosclerosis, arthritis, hypertension, diabetes, nephritis, etc.); of these patients 236 (42.3 percent) were heavy smokers. The above statistical data failed to establish any definite correlation between smoking and cancer of the respiratory tract, and Hoffman attributed these negative findings to small groups, to the poor histories, and to the presence of other etiological factors. Hoffman concluded that smoking increased the liability to cancer of the mouth, throat, esophagus, larynx and lungs, but admitted that the problem is complicated by other factors, particularly syphilis and defective dental conditions, in the absence of which smoking is much less likely to result in cancerous afflictions. He further stated that some attention should be paid to the gross amount of air pollution which in some cases may injuriously affect even non-smokers.

It may be stated in criticism of Hoffman's statistics that (in lung cancer patients) that ~~the finding~~, the finding ~~of~~ 67 percent were smokers is based on only 27 cases. In comparing this figure with percentages for normal males and those with non-cancer, chronic diseases no correction for age distribution seems to have been made, and no mention was made of the duration of smoking.

Bogen and Loomis (1932) found only one instance of bronchogenic carcinoma at autopsy in a women at the Olive View Sanatarium. She had a history of excessive smoking of cigarettes for more than fifteen years. Brockbank (1932) in a series of 62 lung cancer cases reported 9 (14.5 percent) smoked excessively, 6 smoked thick twist: however, 13 (21 percent) had never smoked at all.

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McNally (1932) attempted to correlate the ~~coincidental~~ increase in smoking with the increase in lung cancer. He ~~xxxxxxxx~~ pointed out that between 1905 and 1930 in the United States cigarette consumption increased 34 times (from 3.7 to 123.8 billion cigarettes per year). During this interval the use of cigars declined by 17 percent (from 7.6 to 6.3 billion cigars per year). On this basis, McNally attributed the increase in cancer of the lung to the increase in the use of cigarettes. Hoffman (1931) had earlier suggested a similar comparison, and Müller (1940), ~~and~~ Kennaway and Kennaway (1947), Doll and Hill (1950), and Dungal (1950) among other workers have ~~xxxx~~ noted the parallelism between the reported increase in the incidence of lung cancer and the increase in the consumption of tobacco or of cigarettes.

Ferrari (1933) stated that in in the region of Trieste the number of cases of lung cancer in males surpassed by far the number of cases seen in females. However, in in those lung cancer cases in females that were autopsied characteristic blackening of the lung alveoli due to smoking was observed. He noted that in Trieste where the consumption of tobacco percentage-wise was the highest among all the provinces of Italy, the incidence of lung cancer was also relatively the greatest.

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STUDIES OF Lung CANCER AND THE USE OF TOBACCO, 1935-1939:

Lickint (1935) investigated the smoking habits of lung cancer patients by personal interview, and reported that of 36 male bronchial cancer patients only two were non-smokers. All of 34 smokers smoked heavily, usually cigarettes, with the exception of 3 who were moderate smokers. Of seven female lung cancer patients, only one was a smoker but three others lived in apartments heavily laden with the smoke of male smokers. Lickint called attention to the observation of Schönherr (1928) that exposure to tobacco smoke in the home might be an etiologic factor in lung cancer in women. Lickint felt that as lung cancer occurs in both men and women who are non-smokers, carcinogenic factors other than tobacco must be involved. He also concluded that the smoking of tobacco is of importance in the development of lung cancer generally, and has special importance in the marked increase in the incidence of this condition in males recorded in recent years. He added that the habit of inhaling tobacco smoke should be discouraged and he advised against smoking by members of cancer-disposed families.

Husted and Biilmann(1935) found in a group of 34 lung cancer patients, only 4 inveterate smokers.

Lickint (1935) pointed out that smoking of opium among the Chinese and other Oriental peoples involves inhaling deeply of smoke. He stated that Strauss (1935) had indicated in fact that a high incidence of lung cancer does occur in Chinese opium smokers. Thys (1935) stated that he had found the majority of his lung cancer cases to be heavy smokers, especially of cigarettes.

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Arkin and Wagner (1936) found 90 percent of a series of 135 lung cancer cases were chronic smokers, and concluded that the inhalation of tobacco smoke might be an important factor in producing chronic irritation in the bronchi. Fleckseder (1936) observed that in a series

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of 62 lung cancer cases of the 54 males, 52 were smokers, and of these 37 were heavy smokers, and of the 8 females, all were strong smokers.

Cramer (1937) concluded that tobacco smoking was a factor in the genesis of bronchiogenic carcinoma. He pointed out that a cigar weighing 5 grams yielded 200 milligrams of tar, while an eight-hour drive ten meters behind an automobile resulted in the collection of only 1.5 milligrams of tar.

Simons (1937) discussed tobacco smoke as a possible cause of carcinoma of the lung, but did not consider it an important etiologic factor. Straad (1938) reported that of 140 cases of lung cancer seen in Prague, 65 were smokers, and of these 20 smoked heavily.

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Klotz (1938) after reviewing the literature associating tobacco smoking with the incidence of lung cancer concluded:

> "... it is more than likely that smoking is of absolutely no importance. The available statistics are open to far too many objections to bear any weight. Bronchial cancer is common among non-smokers, and indeed Brockbank found that 14.5 percent of his cases were heavy smokers, while 21 percent were non-smokers. Furthermore, if smoking was a factor of any importance, it is probable that a striking change in sex incidence would have been observed owing to the rapidly growing prevalence of the habit among modern women".

In 1939, the Metropolitan Life Insurance Company (Anonymous, 1939) reported a study of the incidence of cancer of the lung and pleura among its policy holders. It was pointed out that the evidence ~~afforded~~ concerning the possible etiologic role of tobacco smoking in the development of lung cancer fell far short of being convincing. It was stated further:

> "... As regards smoking, for example, it is a matter of common knowledge that the habit since 1917 has become relatively more prevalent among women than among men. If smoking were of appreciable etiological significance, we might expect the death rate for the disease to increase more rapidly among women than among men ... the reverse has actually been the case. At present it appears doubtful that smoking is a factor of etiological importance in cancer of the lung."

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MÜLLER'S STUDY OF SMOKING HABITS OF LUNG CANCER CASES, 1940:

Müller (1940) studied the smoking habits of lung cancer patients. He based his study partly upon detailed case histories and the personal questioning of patients, but largely upon answers to questionnaires sent to surviving relatives. As most lung cancer patients reduce their smoking during the active state of the condition, he asked relatives as to the deceased's smoking habits over an earlier period, and also asked about the occupations of the deceased and about his possible exposure to fumes, dust, and polluted air. Müller took one cigar as equivalent to 5 grams of tobacco and one cigarette as equivalent to 0.8 grams of tobacco. He divided smokers into several classes: Extreme smokers, 10-15 cigars, more than 35 cigarettes, or more than 50 grams of pipe tobacco daily; very heavy smokers, 7-9 cigars or 26-35 cigarettes or 36-50 grams of tobacco; heavy smokers, 4-6 cigars, 16-25 cigarettes or 21-35 grams of tobacco; moderate smokers, 1-3 cigars, 1-15 cigarettes, or 1-20 grams of pipe tobacco; and non-smokers.

Müller presented case histories for 96 cases of lung cancer. Of these 96 cases, 86 were males, and were analyzed as to smoking habits. Twenty-five cases (29.07 percent) were extreme smokers; 18 cases (20.93 percent) were very heavy smokers; 13 cases (15.12 percent) were heavy smokers; 27 (31.29 percent) were moderate smokers; and 3 cases (3.49 percent) were non-smokers. Müller also presented for comparison the smoking habits of 86 normal males of the same age group as the lung cancer cases: Four (4.65 percent) were extreme smokers; 5 (5.81 percent) were very heavy smokers; 22 (25.58 percent) were heavy smokers; 41 (47.68 percent) were moderate smokers, and 3 males (16.28 percent) were non-smokers. The total daily consumption of tobacco by the 86 male lung cancer cases was estimated to be 2900 grams; in contrast, the 86 non-cancer males of similar age consumed about 1250 grams of tobacco daily.

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Müller (1940) concluded that tobacco smoking may be an important causal factor in lung cancer, and that the rise in lung cancer incidence could be traced to the rise in tobacco smoking, especially in the use of cigarettes. However, he granted that as about one-third of the patients were either moderate smokers or did not smoke, other cancer-producing factors must be at work. He pointed out that in his series all lung cancer cases who had worked in relatively unpolluted air (office workers, merchants, innkeepers, etc.) were heavy smokers without exception. On the other hand, in the cases of lung cancer developing in moderate smokers or non-smokers, it was possible to detect some occupational effects upon the respiratory tract. Müller stated that the inhaling cigarette smoke should be discouraged, and that persons from families with cancer histories or individuals with chronic catarrhs of the respiratory tract should be dissuaded from smoking.

CRITICISM OF MÜLLER'S STUDY:

Huismann (1943) analyzed critically and at some length the study of Müller of the smoking habits of lung cancer cases. In the first place, he questioned the soundness of the far-reaching conclusions of Müller because they were based on data for only 86 lung cancer cases and 86 normal males. Further, of a total of 96 cases of lung cancer studied by Müller, 10 were women, and none of these were smokers. Also, the objectivity of Müller's study is questioned because most of the data on the smoking habits of the lung cancer cases were obtained not from the cases themselves, but from surviving relatives, their cases following their death. Huismann emphasized the untenability of Müller's conclusion that cigarette smoking was of special etiologic significance in lung cancer. Actually, more of Müller's lung cancer cases were smokers of cigars and pipes than of cigarettes. For example, of 25 extreme smokers, only 9 were cigarette smokers; of 18 heavy smokers, only 10 were cigarette smokers; and of 27 moderate smokers, only 7

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

STUDIES OF ROFFO, 1931-1941:

Roffo (1931b) reported that in a series of ~~patients with cancer~~ laryngeal cancer cases, ~~larynx~~, 92 percent were strong and only 8 percent weak smokers.

Roffo (1937a) reported that he had seldom seen women with cancer of the mouth, larynx, or lungs. During a 12-year period, the few women with cancer of these sites seen were heavy smokers. During the same period, of 5,000 female cancer patients seen, only 42 had suffered cancer of the ~~so-called~~ "smoking tract", and all of these latter patients were heavy smokers. ~~Roffo presented detailed case summaries of each of these 42 women.~~ Cigarettes of black tobacco were smoked by 45 percent of these women, cigars of black tobacco by 44 percent and pipe tobacco by 12 percent ~~of the patients~~.

Roffo (1939d) stated that in the observations of 78,000 patients (~~presumably all with cancer~~) the following facts merited emphasis: cancer of the smoking tract ranked first in ~~regard to~~ the frequency of malignancies seen and this type of cancer in ninety percent of the cases was found in smokers; cancer of this localization was rarely found in women, and the few exceptions ~~who~~ were smokers.

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Roffo (1941a) reported on the percentage of smokers and non-smokers among the cancer cases of various localizations seen by him during the period 1934-1936. His data are reproduced in the following table:

CANCERS OF THE SMOKING TRACT DIVIDED AS TO SMOKERS AND NON-SMOKERS (ROFFO, 1941a)

	Localization	Year	% Smokers	% Non-Smokers
Single	Larynx	1934	100	0
	Larynx	1935	99.21	0.79
	Larynx	1936	98.56	1.44
Single	Lung	1934	100	0.
	Lung	1935	96.55	3.45
	Lung	1936	94.94	5.06
Single	Tongue	1934	92.20	7.80
	Tongue	1935	88.68	11.32
	Tongue	1936	86.83	13.17
Single	Lip	1934	92.04	7.96
	Lip	1935	90.16	9.84
	Lip	1936	90.73	9.27
Single	Mouth	1934	81.81	18.19
	Mouth	1935	88.45	11.55
	Mouth	1936	99.98	0.02

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Roffo (1941a, 1941c) ~~has~~ stated that clinical observations have revealed that about 95% of the lung, laryngeal and pharyngeal cancers occur in smokers, and that the few cases among women studied at the University Institute for Experimental Medicine and the study of treatment of cancer in Buenos Aires were also heavy smokers. ~~According to this worker, mortality among smokers who were cancer patients mounted from 148 in 1926 to 513 in 1937.~~

He [redacted] the following statistics on the incidence of cancers of the smoking tract seen in Buenos Aires:

MORTALITY FROM CANCER OF SMOKING TRACT (ROFFO, 1941a)

Year	Number	Year	Number
1926	148	1934	496
1927	200	1935	468
1928	207	1936	498
1932	335	1937	513
1933	397		

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STUDIES OF CANCER AND THE USE OF TOBACCO, 1940-1943.

Myers (1940) pointed out the enormous increase in the number of cigarettes consumed in the United States and expressed the view that "the smoking habits unquestionably increase the liability to cancer of the mouth, throat, esophagus, the larynx and the lungs".

Ewing (1940) stated that tobacco has "a predominant influence in the development of cancer of the buccal mucosa". He considered tobacco a contributory factor in cancer of the larynx, esophagus and lung.

Menne and Anderson (1941) concluded:

> "Certainly the striking predominance of bronchiogenic carcinoma in men ... suggests either that in the industries men come in contact with an irritating substance or that the increased consumption ... of tobacco ... is of great significance. It would seem that more careful recordings of the histories to how much particular persons smoke would be of great value in determining the causal relation of the use of tobacco to bronchiogenic carcinoma. The average inquiry simply elicits information that the patient is or is not a user of tobacco."

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Sr. (1938, 1941)

A. E. Roffo ~~in 1941~~ studied the carbon monoxide content of the blood of cancer patients, ~~with cancers.~~ He reported that non-smoking cancer patients living in the open country ~~and being non-smokers~~ showed no carbon monoxide in their blood as determined ~~by a~~ spectrographic allyl- ~~method.~~ Carcinoma patients who were smokers ~~have~~ and who lived in the open country were reported to have traces of carbon monoxide in their blood. Cancer patients living in towns who smoke showed blood carbon monoxide levels from 0.018 to 0.057 percent, while those who were non-smokers showed no or mere ~~near~~ traces of carbon monoxide. Healthy persons from towns who were smokers showed traces of carbon monoxide, while those who ~~were not~~ were non-smokers showed no carbon monoxide in the blood. This worker concluded that carbon monoxide can be found in cancer patients exposed ~~either to~~ to two sources, tobacco smoke and ~~the tobacco smoke from tobacco than~~ to city air, and ~~found~~, that the carbon monoxide blood level is lower in those who are exposed to the influence of only one of these sources. Roffo stated that although the ~~established~~ carbon monoxide blood levels observed ~~quantities are~~ were far below the toxic dose, the ~~state of a~~ slow and chronic asphyxia ~~which they provoke~~ created ~~is not to be undervalued as it~~ might possibly ~~may~~ prepare the biological ground for cancer production or stimulate the growth of ~~already~~ existing ~~cancers.~~ carcinomata.

Jackson and Jackson (1941) reported that 95 per cent of men with cancer of the ~~lung~~ larynx were smokers. In spite of this apparently high percentage of smokers, they ~~did not~~ considered smoking only one of the minor causes of cancer of the larynx. They ~~did~~ did not regard it as an essential cause (Jackson and Jackson, 1937).

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Heerman (1943) reported that of 30 cases of layrngeal carcinoma, 26 cases were habitual and in part very heavy smokers. Eighteen of these cases inhaled the smoke. He also recorded that one of ~~two~~ identical twins, age 48, developed a carcinoma of the vocal cords. The twin with the cancer was a smoker who inhaled and who worked in ~~a armory~~. His twin brother was a tobacco chewer and was a retired miner who suffered from asthma.

Grace (1943a, 1944) reported his clinical observations with patients with lung cancer seen at two municipal hospitals in New York ~~City~~. He stated that they were almost all men, and almost all heavy cigarette smokers who inhaled. He reported three cases in detail, all of whom were heavy smokers and inhalers for over a period of at least fifteen years. Grace also discussed at length the work of Roffo on the actions of tobacco tars on animals and extrapolated the latter's findings to human ~~lung~~ cancers,

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Huismann (1943) discussed at length the parallelism between tobacco consumption and the incidence of lung cancer in Holland. Earlier, Müller (1940) among other workers, had called attention to the tremendous increase in the consumption of cigarettes during the same period in which the increase in the incidence of lung cancer was so extraordinary. Huismann commented that the per capita consumption of tobacco in Holland is recognized to be the greatest [redacted] in the world, and that therefore if any relationship between tobacco consumption and lung cancer can be established, statistically, it should be evident in the data for Holland. Huismann presented the following table based on data for Holland of the Central Statistical Bureau of Hague:

PER CAPITA CONSUMPTION (All forms) TOBACCO USE IN HOLLAND (HUISMANN, 1943)

Year	Per Capita Tobacco Use in kg.	Year	Per Capita Tobacco Use in kg.
1852-1856	1.78	1919	2.97
1857-1861	2.89	1920	4.62
1862-1866	2.38	1921	3.77
1867-1871	2.46	1922	2.78
1872-1876	3.39	1923	3.15
1877-1881	3.23	1924	3.03
1882-1886	3.59	1925	-
1887-1891	3.28	1926	3.47
1892-1896	3.19	1927	3.28
1897-1901	3.14	1928	3.38
1902-1906	3.02	1929	3.45
1907-1911	3.01	1930	3.29
1912	2.84	1931	3.55
1913	3.50	1932	3.54
1914	2.95	1933	3.84
1915	2.06	1934	3.24
1916	2.46	1935	2.98
1917	-	1936	3.07
1918	1.33	1937	3.24
		1938	3.16

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Huismann (1943) concluded that this table makes it clear that in Holland no pronounced increase in the use of tobacco has occurred since the 1870's. He concluded that in view of this finding there are no grounds to suggest a relationship between the increase in cancer, lung cancer in particular, since 1870 and the total consumption of all forms tobacco. Huismann also considered the increase in cigarette and cigar smoking and the alleged relationship to the incidence of lung cancer. He presented the following data taken from the Central Statistical Bureau of Hague:

TOBACCO CONSUMPTION IN HOLLAND (HUISMANN, 1943)

Year	Per capita Smoking & Chewing Tobacco kg. Per Person	No. of Cigars Per Person	No. of Cigarettes Per Person
1921-1925	1.68	144	298
1926	1.68	153	317
1927	1.56	158	342
1928	1.53	165	363
1929	1.45	173	409
1930	1.47	174	455
1931	1.54	171	444
1932	1.59	167	450
1933	1.55	171	476
1934	1.26	171	471
1935	1.25	170	476
1936	1.29	172	467
1937	1.26	174	506
1938	1.16	179	549

From this table it can be seen that the consumption of cigars and cigarettes in Holland has increased on a per capita basis during the period 1926 through 1938; cigars from 153 per person in 1926 to

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179 in 1938; and cigarettes from 317 per person in 1926 to 549 in 1938. Huismann questioned, however, whether this increase in cigarette and cigar consumption can be correlated with the increased mortality from lung cancer on the following basis.

Huismann, following the data of Vaandrager, observed that lung cancer cases are most common in the age group 50-60 years, while according to Dutch mortality figures the most frequent age at death from all causes is in the range 60-70 years. Further lung cancer is only rarely seen before age 40 and first attains importance as a cause of death in the age group 45-49. He further observed that the age at which smoking is usually begun by youths is about 15-16 years, and that lung cancer is seldom seen until some 25-26 years later (that is, after the 40th year), and it may much later after 45-48 years (that is, in the age group 60-64 years). Thus, in 1938 a man dying of lung cancer and being 40-44 years of age would have started smoking in the period 1909-1913, and in the age group 60-64 years, would have begun smoking in the period 1890-1894. These dates are clearly earlier than the tremendous rise in cigarette consumption. Huismann concluded on this basis that the alleged causal relationship between the increased incidence of lung cancer and increased cigarette smoking was unfounded. He also pointed out that in Holland in the period 1931 to 1939 for women the standardized mortality from lung cancer per 100,000 persons increased from 3.55 to 5.03 and he doubted whether this increase in lung cancer in women in such a short span of time could be due to any increase in the number of female smokers.

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ANTI-TOBACCO CAMPAIGN BASED ON ALLEGED Neoplastic CARCINOGENIC ACTION:

In 1942, an anti-tobacco campaign was [redacted]y organized in the secondary and normal schools of Argentina by the Ministry of Public Instruction (Anonymous, 1942). This campaign was [redacted] based on the alleged carcinogenic action of tobacco, and was initiated with the support of A. H. Roffo. The work of Roffo on the induction of neoplasms in animals by tobacco tar has been reviewed earlier in another survey. The success or extent of this anti-tobacco campaign is unknown to the present reviewer.

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SCHAIRER AND SCHÖNIGER'S STUDY OF SMOKING HABITS, 1943.

Schairer and Schöniger (1943) studied the smoking habits of 195 cases of primary cancer of the lung, ~~with regard to the extent of tobacco smoking~~. They also studied the smoking habits of gastric cancer cases, ~~the~~ rectal and prostate cancer cases, and of normal males of age 53-54 years. The data for the cancer cases ~~was~~ were gathered largely by sending questionnaires to close relatives of the deceased, and 50 to 60 percent of all questionnaires were returned in satisfactory form. Inquiries were always made in the case of the lung cancer cases as to the occupation and living conditions of the deceased. For statistical evaluation, the smokers were divided into groups (similar to the scheme of Lickint and of Müller): moderate smokers, 1 cigar or up to 5 cigarettes a day; ~~average~~ mediocre smokers, 2 cigars or 6-10 cigarettes a day; ~~strong~~ heavy smokers, 3 or 4 cigars or 11-20 cigarettes a day; very heavy smokers, over 4 cigars or 20 cigarettes a day. The following table summarizes the data of Schairer and Schöniger, the strong and very strong smokers being combined:

~~PERCENTAGE~~ 670 DIVISION OF TOBACCO SMOKERS ACCORDING TO TYPE OF CANCER AND IN THE NORMAL MALE POPULATION AGE 53-54 (Schairer + Schoniger, 1943)

	Non-Smoker	Moderate Smoker	~~Average~~ Mediocre Smoker	~~Strong~~ Very ~~Strong~~ Heavy Smoker
Lung Cancers:	3 ± 1.8	12 ± 3.7	33 ± 4.9	52 ± 4.7
Gastric Cancer:	16 ± 3.3	43 ± 4.5	20 ± 3.6	21 ± 3.5
Rectal and Prostate cancer:	12 ± 3.8	32 ± 5.4	18 ± 4.6	38 ± 5.7
All Male Cancers:	10.7 ± 1.7	28.4 ± 2.6	24.2 ± 2.4	36.7 ± 2.7

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	Non Smoker	Moderate Smoker	Medium Smoker	Heavy - Very Heavy Strong - Very Strong Smoker
Normal Males (age 53-54)	15.9±2.2	36.3±2.9	21.1±2.5	26.7±2.7

Schairer and Schöniger pointed out that in the case of lung cancer only 3 percent were non-smokers and that 52 percent were strong and very strong smokers. In the gastric cancer series in contrast there were few strong smokers, and many non-smokers and moderate smokers. Schairer and Schöniger stated that they felt that the number of non-smokers (15.9%) observed with normal males age 53-54 was somewhat higher than earlier workers had reported. They suggested that due to the war-time conditions prevailing in Germany, some heavier smokers might be reluctant to return the questionnaire sent to them. However, Schairer and Schöniger felt that the differences in smoking habits between lung cancer patients on one hand and gastric cancer patients and the normal population on the other were statistically significant.

Schairer and Schöniger (1943) compared their findings and the earlier findings of Müller (1940), and presented the following table:

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PERCENTAGE OF TOBACCO SMOKERS IN COLOGNE (MÜLLER) AND JENA (SCHAIRER AND SCHÖNIGER)

36.04

Smoking Habits	Lung Cancer		Normal Men	
	Cologne	Jena	Cologne	Jena
~~STRONG~~ Heavy Smoker (11 or more cigarettes)	65.12	52	36.04	26.7
MODERATE Smokers (1-10 cigarettes)	31.19	45	47.68	57.4
NON-Smoker	~~35.49~~ 3.49	3	16.78	15.9

16.78

Schairer and Schöniger concluded that heavy smoking must be assumed to be ~~a~~ one of the causes of the increase ~~in~~ incidence of lung cancer ~~incidence~~, ~~or at any rate, it could be one of the causes of this increase~~. Schairer and Schöniger admitted, however, that lung cancer was occasionally seen in non-smokers. They pointed out that possibly smoking ~~of~~ ~~possibly~~ affects ~~and~~ an already existing tendency to lung cancer ~~tendency~~ to bring it to full development.

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STUDIES OF LUNG CANCER AND THE USE OF TOBACCO, 1944-1947

Potter and Tully (1945) reported on the smoking habits of 2,927 males over 40 years of age who were patients at the cancer clinics of Massachusetts. These patients were classified into those who used no tobacco, those who reported slight use, moderate use, and excessive use. Potter and Tully in their article do not define this classification scheme any more closely than this. Morbidity rates were computed for each smoking class associated with cancer of the buccal cavity, digestive tract, respiratory tract, skin, and for cancer of all other sites. The data of Potter and Tully are summarized in the following table:

SMOKING HABITS OF CANCER CASES
(Potter and Tully, 1945)

Extent of Tobacco Use	No. of Males	RATE PER 100 BY SITE				
		Cancer of Buccal Cavity	Cancer of Digestive Tract	Cancer of Respiratory Tract	Cancer of Skin	Cancer of All Other Sites
None	655	3.7	5.6	0.5	11.3	5.5
Slight	357	8.1	9.5	1.1	7.8	7.8
Moderate	1155	11.5	8.3	2.0	12.5	5.2
Excessive	760	17.9	5.8	1.7	13.0	4.6

These workers concluded there was a definite association between cancer of the buccal cavity and the use of tobacco. They also concluded that it there appeared to be some association between the use of tobacco and cancer of the respiratory tract.

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Clerf and ~~Norbert~~ Herbut (1946) stated that, "Irrespective of being an etiologic factor [in lung cancer], smoking, more than anything else, contributes to delay in diagnosis by masking a common, early and important symptom; namely, cough."

Clemmesen and Busk (1947) analyzed the data of the Central Tuberculosis Station of Copenhagen regarding the age distribution of primary cancer of the lung over a period of years. The concluded that even if they allowed for the small absolute values of the figures, there has not been an increased morbidity rate for lung cancer in the young. They felt that such an increase was to be expected if increased inhalation of tobacco smoke is a factor in the development of lung cancer, unless the assumption is made that a latent period for lung cancer of about two decades is operating.

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Kennaway and Kennaway (1947) reported on the incidence of cancer of the lung and larynx based upon data derived from the cases of death certificates of cancer of the lung and larynx in males from England and Wales for the period 1921-1938. These workers found no special occupation among the 63 examined, to which the increase in the total number of cases of lung cancer could be attributed. The Kennaways pointed out that the high mortality of cancer of the lung in towns, the low mortality in agricultural occupations, and the absence of social gradient have been pointed out as compatible with an etiologic factor in the air such as coal smoke. On the other hand, these workers suggested that these factors might also be explained by assuming an etiologic role for tobacco consumption. They pointed out that the absence of social gradient in the incidence of lung cancer would be well explained by the parallel absence of social gradient for the tobacco habit. These workers reported that during the period 1933-1938 the incidence of cancer of the lung was no higher in those engaged in the preparation and sale of tobacco than in the general population; however, the incidence in these workers had been slightly higher than that of the general population in the earlier period 1921-1932.

STUDIES OF LUNG CANCER AND THE USE OF TOBACCO

Churchill (1948) observed that nothing is known about the cause of cancer of the lung that can be translated into effective preventive measures. He further stated that a knowledge about nature and the mode of action of carcinogenic agents, and a careful recording of the smoking habits of ample numbers of patients with the disease,

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provide no factual evidence for the assumption that cigarette smoking might be a causative agent in the development of cancer of the lung.

Wassink (1948) studied the occupations and tobacco habits of 143 cases of pulmonary cancer. In this series, there were 136 males and 7 females. He concluded that pulmonary cancer occurred chiefly in intellectuals and white collar workers and seldom in agricultural workers. He also observed that lung cancer cases showed the highest degree of addiction to tobacco of all cancer cases. In a series of laryngeal cancers, similar findings were reached but less definite in magnitude. Wassink concluded that tobacco smoking and exposure to smoke-laden air were the foremost exogenous factors in pulmonary cancer in men in Holland.

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Jones (1949) found eight non-smokers in 82 patients with proved carcinoma of the lung, compared with eleven in a corresponding group of patients with diseases other than cancer. There were twenty-eight heavy smokers in the cancer group, against fourteen in the comparative group.

Morelli (see DeFrancis, 1950) observed in an interview that at least 90 percent of the cases of primary lung cancer seen by him were heavy smokers, and not of pipe or ordinary cigars, but of cigarettes. He added that in the majority of these cases, they were smokers of cigarettes of American origin. He observed that this association seemed to surpass the limit of possible coincidence, and suggested that cigarettes rather than tobacco in general might be involved in lung cancer. He felt that additional research was necessary to establish whether this is due to some special "seasoning" of cigarettes or rather from the paper. He commented that it is easy to wonder whether or not the paper in cigarettes produces tar residues which might act as carcinogens. In conclusion, Morelli observed that his observation constituted "only a suspicion; a suspicion which nevertheless stimulates one towards establishing the truth".

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Valdoni (1950) in a recent paper appeared somewhat skeptical of the relation between cigarette smoking and cancer. However, he held that influenza virus might remain in an intracellular stage for decades and by accidental stimulation (such as tobacco) might become reactivated and in the face of declining hormonal equilibrium might give rise to cancer.

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Ochsner (1950) stated that he was convinced that the increased incidence in bronchiogenic carcinoma is due to the increased use of cigarettes, and held that there is evidence that tobacco contained substances which are carcinogenic.

Ochsner (see Anonymous 1950g, 1950h, Kaempffert, 1950; Plakeslee, 1950) in a paper of which M. E. Debakey and P. T. Decamp were co-authors, presented before the Fifth International Conference on Cancer, stated:

> "It appears without doubt that inhalation of cigarette smoke exerts a carcinogenic ... effect upon lung tissue ... It can be predicted that if cigarette smoking continues at the present rate, or if it increases as it has in the past, the future incidence of bronchogenic carcinoma will be many times that of other cancers of the body."

Gall (1950) in commenting on the sudden increase in carcinoma of the lung after the end of the first decade of the present century observed that during the greater part of the last century and at least the earlier years of this one, men in debilitating climates chain-smoked strong cheroots, yet carcinoma of the lung was a rarity.

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STUDY OF DUNGAL, 1950:

Dungal (1950) has discussed at length the incidence of lung cancer in Iceland as contrasted with European countries and the United States. His survey showed that in Iceland lung cancer is still a rare disease, the observed incidence being similar to that existing in many European countries at the beginning of the century. This worker concluded that respiratory infections including influenza and the existence of tarred roads were unlikely as etiologic factors in the genesis of lung cancer in Iceland. He called attention to the marked difference in the per capita consumption of tobacco, particularly in the form of cigarettes, between Iceland and most European countries and the United States. Dungal presented the following data (partially taken from Hutson, 1937):

RETAIL SALES OF CIGARETTES/PER HEAD (TOTAL POPULATION)

Country	1913	1920	1924	1929	1932	1940	1945	1946	1947
Austria	[illegible]	0.87	1.20	1.57	1.85				
Finland	0.28	1.36	1.47	1.75	1.33				
France	0.42	0.38	0.37	0.86	0.97				
Germany	0.80	0.72	0.90	1.12	1.06				
Hungary	—	—	0.35	0.60	0.66				
United Kingdom	0.71	1.49	1.73	2.26	2.33				
Iceland	0.03	0.14	0.24	0.40	0.53	0.44	1.00	1.50	1.39

Dungal observed that in England where the incidence of lung cancer seems to be the highest in Europe, there is the highest consumption of cigarettes, and the annual total has increased greatly between 1923 and 1935. He further recommend that, assuming that lung carcinoma is

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determined by the inhalation of tobacco smoke during a period of 15 to 25 years, then 1913-1935 would correspond to the pre-paratory period for the lung carcinomas that have been making themselves increasingly apparent in the last two decades. This worker further compared the per capita consumption of cigarettes in Iceland with that in other countries (see table above) and observed that in most of Europe it increased steadily between the two world wars, whereas in Iceland the figure was relatively low until the beginning of the second World War, when it rose enormously and is apparently still increasing rapidly. Before 1926, the consumption in Iceland was under 0.24 lbs. per person, in the first two decades of the century, it was considerably less. [illegible] (1950) argued that assuming 20 to 25 years of tobacco smoking is necessary to produce cancer in the lung, a very low rate of lung cancer should be expected in Iceland until 1960-1965, when the rate should rise very considerably.

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STUDY OF SMOKING HABITS BY LEVIN AND CO-WORKERS, 1950:

Levin, Goldstein, and Gerhardt (1950) reported a study of the tobacco habits of patients with cancer of the smoking tract. Since 1938 a history of tobacco usuage has been obtained routinely from all patients admitted to the Roswell Park Memorial Institute of Buffalo. These histories (date smoking begun, duration, type, and amount) were a part of the regular clinical history taken before the final diagnosis had been established. Approximately one-half of the patients admitted to this institute were subsequently found not to have cancer. The workers felt that as no special attention to the history of smoking had been paid to any single type of illness, the records could be presumed to be relatively free from bias which might result from any preconceived ideas as to the relation between smoking and a particular form of cancer. The study was based on 1,045 male cancer patients and 605 non-cancer patients. The cancer sites selected were lung (236 cases), lip (143 cases), pharynx, esophagus, colon, rectum, and a scattered number of other sites. The non-cancerous patients had symptoms referable to the same sites, but which proved not to be due to cancer.

Levin and his co-workers found that over eighty percent of all patients (cancerous or non-cancerous) were smokers. The prevalence of smoking in all of its forms (whether cigarette, pipe, and or cigar) did not vary strikingly with age past the age of 25 years but the prevalence of cigarette smoking decreased with age, and that of pipe and cigar smoking increased with age. These workers pointed out that comparisons of groups with different age compositions would therefore show different proportions of cigarette, pipe and cigar smokers because of the above factor alone. They

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therefore based comparisons on prevalence rates, standardized for age by applying the age-specific rates to the entire 1,650 patients. The original article should be consulted for the statistical details of this procedure.

Levin and his co-workers found that there were more smokers among cancer patients than non-cancer patients, because of an excess of cigarette and pipe smokers among the former group. Further analysis with regard to the site of the cancer, indicated that this excess was due entirely to the increased percentage of pipe smokers among cases of cancer of the lip and to the increased percentage of cigarette smokers among cases of cancer of the lung. Further , these differences were confined to those who had smoked cigarettes or pipes for 25 years or longer. These workers failed to find comparable differences in smokers of less than 25 years' duration, and suggested that this failure may have been due to the relatively small percentage of such smokers which may be expected in the older population.

Levin and his co-workers found that there were more than twice as many cases of lung cancer in those who had smoked for more than 25 years than among other smokers or non-smokers of comparable age. Pipe smokers and cigar smokers were reported to have no more cancer of the lung than did non-smokers. Lip cancer was significantly higher in pipe smokers but not in cigarette smokers as compared to the hospital patient population. However, lip cancer was increased among cigar smokers. Levin and co-workers stated that no other site of cancer that was included in their study was found to be associated with any particular type of smoking. However, not all sites of cancer were studied. These workers concluded:

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"These data indicate that, in a hospital population, cancer of the lung occurs more than twice as frequently among those who have smoked cigarettes for 25 years than among other smokers or non-smokers of comparable age. Pipe smokers apparently experience an almost equal increase in the incidence of lip cancer, compared with other smokers or non-smokers. It is somewhat surprising to find that the type of smoking, i. e., cigarettes for lung cancer, pipe for lip cancer, is the associated factor rather than the actual use of tobacco.

twenty-five

→

"The data suggest, although they do not establish, a causal relation between cigarette and pipe smoking and cancer of the lung and lip, respectively. The statistical association may, of course, be due to some other unidentified common factor between these types of smoking and lung and lip cancer."

Levin (1950) in a brief note has restated the above conclusion with the added thought, "the data on smoking and its association with cancer shows only the fact; the reason for it is a subject for further inquiry---".

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STUDY OF SMOKING HABITS BY GRAHAM AND CO-WORKERS 1948-1950:

E. Graham presented a paper on the smoking habits of lung cancer patients before the First National Cancer Conference in 1948. His paper was ~~abstracted~~ reported by Laurence (1948). It is from the latter source that the following material is taken. Graham studied the smoking habits of 200 male lung cancer patients in the age group 40-80 years and the smoking habits of 500 male patients of the same age group who did not have lung cancer. His data showed that of the 200 patients with lung cancer, 95.5 percent had smoked one package of cigarettes a day or more for at least twenty years. Of the 500 patients who were free from cancer, on the other hand, only 50 percent smoked a package or more a day during the past 20 years.

Graham's study also reported that of 200 patients with lung cancer only 0.5 percent were non-smokers, while of the 500 patients studied as controls, 11 percent were non-smokers. According to Laurence (1948), Graham emphasized that no conclusions could be drawn from these studies that cigarette smoking, no matter how heavy, will itself cause cancer of the lung, no matter over how long a period, since fifty percent of the control patients smoked the same amount over the same period without developing a lung cancer. However, all studies pointed to the conclusion that cancer develops because there is a predisposition ~~for~~ to it, either hereditary or environmental. Graham felt that if a susceptibility to lung-cancer already exists, then it is possible that cigarette smoking in excess, over a long period of time, may act as a cancer-producing factor

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Graham also reported a very large difference in the ratio between men and women in the susceptibility to lung cancer, and indicated that a hormonal factor might possibly be responsible for this. However, it was pointed out that it was premature to draw such a conclusion, since it was found that the average duration of smoking in patients with lung cancer was 35 years, which goes back to about the time when women were just beginning to smoke commonly in the United States.

Wynder and Graham (1950) reported a study of the smoking habits of 684 cases of bronchiogenic carcinoma. These workers obtained the data not from hospital records (since it was clear that routine hospital records did not supply adequate answers to questions), but rather largely through personal interviews, using a standard questionnaire. In this study 634 lung cancer patients were directly interviewed. Thirty-three replied through mailed questionnaires and data on 17 were obtained by questioning persons who had known the patient throughout his adult life. As patients entering hospitals with chronic disease of the lungs usually have stopped smoking months or even years before, the average use of tobacco was estimated during the last 20 years of their smoking period. Control patients were similarly questioned, and Wynder and Graham felt that any possible error lying in this method of estimating smoking habits was therefore balanced. The patients were also questioned concerning all occupations and to what types

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of dust or fumes they had been exposed. All the cases studied by Wynder and Graham had their diagnoses confirmed by microscopic examination. Of the 684 cases studied, 605 male and 25 female patients had epidermoid, undifferentiated, and unclassified carcinomas, and 39 male and 15 female patients had adenocarcinomas.

Wynder and Graham, to reduce all bias on the part of the interviewers who saw patients believed to have bronchiogenic carcinoma, conducted a control study in which non-medical investigators interviewed every patient over 30 years of age admitted to the chest service of Barnes Hospital without knowing the diagnosis in advance. When the final diagnosis was determined, all cases of lung cancer (75 men) were separated from the other cases (132). In addition, the same interviewers interrogated patients with cancer of the lung at other hospitals in St. Louis, also without previous knowledge of diagnosis. These non-medical investigators also questioned 25 patients with cancer of the lungs at several hospitals.

To provide a further control, groups of non-cancerous smokers, 780 patients of the general population at several hospitals were also interviewed. An additional 552 female patients without lung cancer were also interviewed.

Wynder and Graham, to make possible statistical analysis of their results possible, utilized the following classification of smoking habits:

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Group 0 .....Non-smokers (less than 1 cigarette per day for more than 20 years)
Group I .....Light smokers (from 1 to 9 cigarettes per day for more than 20 years)
Group II ..... Moderately heavy smokers (10-15 cigarettes per day, more than 20 years)
Group III..... Heavy smokers (16-20 cigarettes per day, more than 20 years)
Group IV ..... Excessive smokers (21-34 cigarettes per day, more than 20 years)
Group V ..... Chain smokers (35 or more cigarettes per day for at least 20 years).

In above classification, Wynder and Graham arbitrarily counted 1 cigar as equivalent to 5 cigarettes, and 1 pipeful of tobacco as equivalent to 2.5 cigarettes. If a patient smoked for less than twenty years, his amount of smoking was adjusted to a twenty-year period, i.e., a patient smoking twenty cigarettes for ten years was classified as smoking ten cigarettes daily, Group II. These workers stated, however, that such adjustments were rarely necessary, since only a few patients had smoked for less than 20 years. In those cases, where a patient had habitually smoked more than one type of tobacco during the last twenty years, the various types were treated additatively in this classification.

Wynder and Graham reported data on the smoking habits of 100 patients with cancer of the lungs and 186 patients with diseases of the chest other than cancer, both groups being interviewed by two non-medical investigators who had no previous knowledge of the diagnosis in a given case, and found no non-smokers among the lung cancer group while there were 14.1 percent non-smokers among the patients with other thoracic diseases. Ninety-five percent of

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the patients with cancer were in the classification of moderate heavy to chain smokers and 53 percent were excessive and chain smokers, while among the patients without cancer 75.3 and 23 percent respectively fell among these smoking groups.

Wynder and Graham further reported the smoking habits of 83 cases of cancer of the lung interviewed independently by four cooperating groups of physicians in various parts of the United States. They found that 2.4 percent of these lung cancer cases were non-smokers and 93.2 percent moderately to chain smokers, while 59 percent were classed as excessive and chain smokers.

Wynder and Graham observed that in their combined series of 605 patients with cancer of the lungs, ~~1.4 percent were non-smokers~~ non-smokers constituted 1.4 percent and the percentage of heavy to chain smokers was 85.2 percent while that of excessive and chain smokers was 49. Since the ~~position~~ distribution of these three series of lung cancer cases ~~according~~ with regard to smoking habits corresponded closely with one another, Wynder and Graham considered findings based on ~~the~~ study of their additive series of 605 cases as representative.

These workers noted that the age distribution of cancer of the lungs in their combined series showed only 2.3 percent of the patients to be under 40 years of age, while 79.3 percent were 50 years or older. On comparing the amount of smoking in 605 patients with cancer of the lungs with that in 780 male patients with other diseases (adjusted to comparable age distribution and economic

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distribution) it was reported that while there were 14.6 percent non-smokers among the patients with other diseases, there were 1.3 percent non-smokers among the male lung cancer patients. While there ~~are~~ were 54.7 percent heavy to chain smokers and 19.1 percent excessive and chain smokers among the general hospital groups, there ~~are~~ were 86.4 and 51.2 percent, respectively, among the patients with cancer. These workers felt that these differences were highly significant and suggested that in general the patients with cancer of the lungs in their forties and early fifties have smoked more heavily than the older patients with this disease. However, this observation did not seem to apply to the few patients in their thirties. The age group 70-79 had the greatest percentage of light and moderately heavy smokers.

Wynder and Graham concluded that the values for the combined results of 605 patients with cancer of the lung, as compared with 780 men in the general hospital population had the probability of a deviation from expectation (p) for various groupings of the smoking in no case greater than 0.0001. These workers stated the following:

> "On the basis of the statistical data for ... the combined results when the non-smokers and the total of the high smoking classes of patients with lung cancer are compared with patients who have other diseases, we can reject the null hypotehsis that smoking has no effect on the induction of cancer of the lungs. If smoking does not have anything to do with the induction of cancer of the lungs, then the observed deviation could occur only with the probability (p) as shown above."

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Wynder and Graham also presented some miscellaneous data on the cigarette smoking habits of the group with cancer of the lung. Nearly all (98.7 percent) of the cigarette smokers, but fewer pipe (62.5 percent) and cigar (18 percent) smokers, stated that they inhaled. Of the cancer patients interviewed, 78.5 percent stated that they usually began to smoke before breakfast. Among the general hospital population, pipes and cigars were smoked more prominently in the older age groups.

Wynder and Graham reported that the duration of smoking in the 605 patients with lung cancer was such that 96.1 percent had smoked for 20 years or more, 85.4 percent for 30 years or more, 68.2 percent for 35 years or more and 50.2 percent for 40 years or more. Only 3 of the patients with bronchiogenic cancer began to smoke after the age of 25.

Wynder and Graham also found that among 39 men with adenocarcinoma of the lung there were 4 non-smokers (10.3 percent), a percentage higher than that found for other types of bronchiogenic carcinoma. There were 7 chain smokers (18 percent) significantly more than in the general male hospital population; 10.3 percent were excessive, 38.5 percent were heavy, 15.4 percent moderately heavy and 7.7 percent light smokers. They concluded that the influence of tobacco smoking on the induction of adenocarcinoma was less marked than with bronchiogenic carcinoma. Among 13 women with adenocarcinoma and two designated as having terminal bronchiolar carcinoma, there was not one heavy smoker; thirteen were non-smokers and two

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light smokers. Among 25 female patients with epidermoid and undifferentiated carcinoma, however, there were 15 smokers of many years' duration as well as 10 non-smokers. Among those who smoked, there were one light, four moderately heavy, six heavy, two excessive and two chain smokers.

These workers also interviewed 552 female hospital patients without cancer of the lung with regard to smoking habits. The data obtained showed that few women in the cancer age have been heavy smokers for many years and that most of the heavy smokers are young women. Of these 552 women, 79.6 percent were non-smokers; 11.3 percent were moderately heavy to chain smokers, and only 1.2 percent of the controls in the cancer age were excessive or chain smokers for at least twenty years.

Wynder and Graham pointed out that since in a small percentage of cases lung cancer occurs in non-smokers and minimal smokers, and since it obviously does not develop in every person who has been a heavy smoker for a long time, that smoking cannot be the only etiologic factor in the induction of the disease.

These workers stated:

> "... the temptation is strong to incriminate excessive smoking, and in particular cigaret smoking, of a long period as at least one important factor in the striking increase of bronchiogenic carcinoma for the reasons: (1) It is rare to find a case of epidermoid or undifferentiated carcinoma in a male patient who has not been at least a moderately heavy smoker formany years; (2) the use of cigarettes is much greater among patients with cancer of the lungs than among other patients

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> of the same age and economic groups; (3) the sex distribution of cancer of the lungs roughly corresponds to the ratio of long-term smoking habits of the two sexes ..., and (4) the enormous increase in the sale of cigarets in this country approximately parallels the increase of bronchiogenic carcinoma."

Wynder and Graham, of course, appreciated that by itself the last observation means little since similar curves could be drawn for many other commodities.

These workers noted that the majority of patients with lung cancer are cigarette smokers rather than pipe or cigar smokers, the ratio being over and above that found in the control hospital population, and suggested that this may be due in part to cigarette smoke being more frequently inhaled that that of either pipes or cigars, partially to the physical and economic convenience (more persons are heavy smokers of cigarettes than of either pipes or cigars), and to certain irritative substances that may be present in cigarettes in greater amounts than in pipes or cigars. With regard to the last consideration, they point out that the role of paper, the use of insecticides during the growth of the tobacco, and the other ingredients warrant further research in this regard.

Wynder and Graham pointed out that if smoking is an etiologic factor in the development of lung cancer, apparently a time lag exists. Cancer of the lung occurred in three cases in which the patient had stopped smoking for ten years or more; these three

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patients had smoked for thirty years or more previously, and none gave a history of occupational or other irritative exposures.

Wynder and Graham in an addendum reported the smoking habits of a few additional cases of lung cancer. In one series of 24 cases of lung cancer there were no non-smokers or light smokers, 7 heavy smokers, 13 excessive smokers, and 4 chain smokers. In a further series of 21 patients, there was one non-smoker (a 72-year old blacksmith), 10 heavy smokers, 6 excessive smokers and 4 chain smokers. They concluded that these additional 45 cases showed the same trends noted in the larger series discussed above.

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STUDY OF SMOKING HABITS BY SCHREK ET AL., 1950

Schrek and co-workers (1950) studied the smoking habits of 82 men with cancer of the lung and 73 men with cancer of the larynx and pharynx and compared these habits with those of a control group of 522 patients with miscellaneous tumors other than those of respiratory and digestive systems. They reported a relatively high percentage of cigarette smokers among the patients with cancer of the respiratory tract as compared to the control group. They concluded that this positive correlation in the incidence of cigarette smoking and the incidence of cancer of the respiratory tract appeared to be both statistically and biologically significant. They stated, "there is strong circumstantial evidence that cigarette smoking was an etiologic factor in cancer of the respiratory tract". These workers found only apparently negative correlations between cigarette smoking and miscellaneous cancers. They found no correlation between the incidence of cigarette smoking and the tumors of the upper digestive tract. The group of patients with tumors of the lung, larynx and pharynx, and the lip continued a significantly higher percentage of smokers (68.3, 69.9, and 62.9 percent, respectively) than the control group of patients (48.8 percent).

In this study of Schrek and co-workers, the arithmetic mean for the ages of the patients with cancer of the lung, larynx and pharynx, and lip, 51.46, 52.57, and 52.72 years did not differ significantly from that for the control group (51.98 years). These workers made a further detailed study and analysis of the percentage

(defined as the use of ten or more cigarettes daily)

the original article should be consulted for discussion of the choice of this particular control group.

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of cigarette smokers and men with cancer of the larynx and pharynx corrected for age and race (negro patients excluded) and concluded:

> "...the percentage of cigarette smokers in men with cancer of the larynx and pharynx is definitely higher than in the control group (P = 0.01). For cancer of the lung, the percentage of cigarette smokers is probably higher (P = 0.03)."

Schrek and co-workers also noted that in patients with tumors in sites other than in the respiratory tract, the older men 50-59 and 60-69 years had a lower percentage of cigarette smokers than men 40-49. They felt that this finding is consistent with the increasing popularity of smoking that might be expected to affect the younger men more than the older.

Schrek and co-workers also concluded from their data that there are no significant differences in the geographic distribution of patients with cancer of the respiratory tract and of control patients.

These workers also investigated the duration and age of onset of smoking in patients with cancers of the respiratory tract and in the controls. They failed to confirm an anticipated longer duration of smoking and an earlier age of onset of cigarette smoking for patients with cancer of the respiratory tract as compared with patients with cancer of other sites.

Schrek and co-workers also presented percentages of light (10 or less cigarettes daily), moderate (10-20), and heavy (more than 20) cigarette smokers for patients with cancer of various sites and in a control group. They concluded that patients with cancer

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of the respiratory tract had a higher percentage of both heavy and moderate cigarette smokers than the control group. They concluded further that their findings lent support to the belief that the association between smoking and cancer of the respiratory tract had biological significance. For cancer of the lung, of the larynx and pharynx, and of the lip, the percentages of non-smokers were less than for other tumors (14.6, 13.7, and 10.3 Percent as compared to 23.9 Percent).

Schrek and co-workers concluded that their correlation between ~~smoking~~ tobacco smoking and cancer of the respiratory tract could ~~not~~ be the result of fortuitous or chance factors, and that their test for statistical significance indicated that the observed results were ~~not~~ due to faulty sampling. They felt that the chance ~~of~~ that the correlation might be an indirect one could ~~can~~ be minimized to a considerable degree by better selection of control groups. ~~Their original paper should be consulted for thorough details.~~ They further concluded although a direct relationship may exist between cigarette smoking and cancer of the respiratory tract, smoking is, at most, only a weak carcinogenic agent. This is based on the mortality statistics of the United States that show only 0.76 percent of the deaths of men past 40 are due to cancer of the respiratory system.

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It is interesting to note that in

~~In criticism of~~ the statistical procedure of Schrek and co-workers (1950), ~~it may be pointed out that~~ when a control group of 5,003 patients selected at random as to diagnosis was employed (54.8 percent of which were smokers), the difference from the ~~percentage~~ percentage of smokers in the lung cancer group (about 68 percent) was not considered statistically significant (P between 0.01 and 0.05). These workers therefore based their analysis on a control group of 522 cancer patients with tumors other than those of the respiratory tract and upper digestive tracts (of which group, 48.8 percent were smokers). With adjustment of the data for age (and excluding Negroes), the percentage of cigarette smokers in men with cancer of the lung was then higher than in the control group (P = 0.03). The choice of this second control group is a departure from other similiar studies, and does not permit easy comparison of conclusions with findings of other workers. In may be noted again that Schrek and co-workers defined "cigarette smoking" as the consumption of ten or more cigarettes daily, a definition not adopted by many other workers.

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STUDY OF SMOKING HABITS BY WATSON, 1950:

Watson (1950) reported a study of smoking habits of lung cancer patients at the Memorial Hospital, New York. The data employed by Watson were also employed in the study of Graham (1948), and Watson makes the following interesting comment:

> "In the United States some recent publicity was given to the subject of smoking in cancer by Dr. Graham's group at St. Louis, and, although it was not mentioned, 100, or 1/2 of the cases studied, came from Memorial Hospital, and the figure as first reported seem to indicate that 97.5 percent of our cases were heavy smokers and none of our patients with cancer were the non-smokers. These figures were widely quoted, but unfortunately they are inaccurate."

In the study of smoking habits at Memorial Hospital, the smoking habits were classified into three groups: non-smokers; moderate smokers (up to 20 cigarettes per day for 20 years or more with inhalation); heavy smokers (20 to 60 cigarettes per day for 20 years or more with inhalation). For purposes of comparison, one type was taken as equivalent to 2.5 cigarettes, and one cigar as equivalent to 5 cigarettes. The findings of Watson are summarized in the following two tables:

SMOKING IN LUNG CANCER, MEMORIAL HOSPITAL, MALES
(From Watson, 1950)

Smoking Classification	Lung Cancer	Control Series
Non-smoker	5 %	11 %
Moderate smoker	58 %	70 %
Heavy smoker	37 %	19 %

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SMOKING IN LUNG CANCER, MEMORIAL HOSPITAL, FEMALES
(From Watson, 1950)

Smoking Classification	Lung Cancer	Control Series
Non-smoker	58 %	60 %
Moderate smoker	25 %	37 %
Heavy smoker	17 %	3 %

Watson (1950) concluded that "Comparison of the smoking habits of victims of lung cancer with those of control cases obtained by careful questionnaire affords strong ground for suspecting the carcinogenic possibilities of heavy, chronic smoking". Watson further stated:

> "Chronic, heavy cigarette smoking may very well be an additive factor in the causation of lung cancer in sensitive individuals. However, the individual irritant itself may not be assignificant as a ~~xxxxxxx~~ chronicity of the patient's exposure to that irritant. In this respect, I suppose we are witnessing a vast human experiment never before carried out by man; namely, what will be the long range result on the human tissues and structures which come in contact with that chronic smoke stream."

The control series employed by Watson in this study seems identical with that reported by Graham (1948), and therefore presumably is based on 500 males in the age group 40-80 years. From the limited data and details reported by Watson, it is not clear that the cancer series has the same age distribution as the control group, or whether the two are of comparable economic distribution.

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STUDY OF SMOKING HABITS BY DOLL AND HILL, 1950:

Doll and Hill (1950) have reported an extensive statistical study of the smoking habits of 649 men and 60 women with carcinoma of the lung and a like number of control patients with diseases other than cancer interviewed by four non-medical investigators at twenty hospitals in London and environs. The non-cancer control group of general hospital patients were chosen so as to be of the same sex and age as the lung carcinoma patients. The control group differed slightly with regard to social class, but in no more than might easily be due to chance (P between 0.3 and 0.5), and also differed significantly with regard to place of residence (P less than 0.001). These workers felt that the latter difference would not invalidate comparisons, especially as, in a briefer series of 98 lung carcinoma patients and 98 controls seen at district hospitals in London this difference in place of residence disappeared.

Doll and Hill (1950) had patients closely questioned on the following points: (a) Had they smoked at any period of their lives? (b) At what ages had they started and stopped? (c) What amount were in the habit of smoking before the onset of the illness which brought them into the hospital? (d) What were the main changes in their smoking history and the maximum they had ever been in the habit of smoking? (e) In what varying proportions had pipes and cigarettes been smoked? (f) Did they or did they not inhale? In this inquiry a smoker was defined as a person who had smoked as much as one cigarette

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a day for as long as one year, and any less consistent amount was ignored. In an attempt to assess the validity of relying on a patient's memory and veracity with regard to his smoking habits, these workers interviewed fifty non-cancer patients, and after an interval of six months of more, interviewed the same patients a second time. The data thus obtained indicated a high degree of consistency in the replies obtained at the two interviews. Doll and Hill concluded that the smoking histories obtained by their interview technique were reliable enough to indicate general trends and to substantiate material differences between groups.

The statistical efforts of Doll and Hill in analyzing their data exceeds by far similar efforts of other recent studies on the smoking habits of lung cancer patients. They examined their data for possible correlations between (a) the proportion of smokers and non-smokers in lung cancer patients and control patients with diseases other than cancer, (b) the most recent amount of tobacco consumed regularly by smokers in these two groups before the onset of illness, (c) the maximum amount of tobacco ever consumed regularly by the smokers of both groups, (d) the estimated total amount of tobacco ever consumed by the smokers of the two groups, (e) the age at starting to smoke, and the number of years smoked, and the number of years stopped smoking in the two groups, and (f) any possible diffdrentiation between the effects of cigarette and pipe smoking in the two groups, and (g) any differentiation between the effects of inhaling in the ~~lung cancer and~~ group

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~~non-cancer control~~ two group. The findings based on these varied methods of evaluating smoking histories are discussed in the following paragraph.

Doll and Hill examined ~~the~~ their data for any association ~~at all~~ between the proportion of lung carcinoma patients who had been smokers and the proportion of smokers in the comparable group of subjects without cancer. Of 649 male lung cancer patients, 0.3 percent were non-smokers, while in the control male group of 649 patients 4.2 percent were non-smokers. The probability that this difference was a chance occurrence was calculated to be 0.00000064. In the case of 60 female lung cancer patients and in a like number of female control patients the respective percentages of non-smokers were 31.7 percent and 33.3 percent. The probability that this difference was a chance occurrence was calculated to be between 0.01 and 0.02. Doll and Hill concluded that the very small proportion of those with carcinoma of the lung who had been non-smokers was ~~most~~ significantly smaller ~~less~~ than the corresponding proportion in the control group, and that in women the habit of smoking was significantly more frequent among those with carcinoma of the lung.

Doll and Hill (1950) also classified the smoking habits of the lung cancer patients and control patients according to the amount they smoked immediately before the onset of the illness which brought them into the hospital; if they had given up smoking before then, they were classified according to the amount smoked immediately prior to giving it up. To permit a common classification of both pipe and cigarette smokers, a conversion factor of ~~1 oz.~~ one ounce of tobacco a week being equivalent

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to four cigarettes a day was assumed inasmuch as there is about one ounce. 1 oz. of tobacco in 26.5 normal-size cigarettes. These workers presented the following tabulation:

MOST RECENT AMOUNT OF TOBACCO CONSUMED REGULARLY BY SMOKERS BEFORE ONSET OF PRESENT ILLNESS; LUNG CANCER PATIENTS AND CONTROL PATIENTS WITH DISEASES OTHER THAN CANCER

(Adapted from Doll and Hill, 1950)

Disease Group (No. of patients)	No. of Cigarettes Smoked Daily: 1	5	15	25	50+
Male Patients:					
Lung Cancers (647)	(5.1%)	(38.6%)	(30.3%)	(21.0%)	(5.0%)
Control with Diseases other than Cancer (622)	(8.8%)	(47.1%)	(30.5%)	(11.4%)	(2.1%)
Female Patients:					
Lung Cancers (41)	(17.1%)	(46.3%)	(22.0%)	(14.6%)	(0.0%)
Control with Diseases other than Cancer (28)	(42.9%)	(35.7%)	(21.4%)	(0.0%)	(0.0%)

Application of the "Chi" test to the data of the above table indicated that the probability (P) of the observed differences in the distribution of smoking habits being a chance occurrence /of male lung cancer patients and male control patients/ was less than 0.001; in the female lung cancer and control patients, the corresponding probability of chance occurrence fell between 0.05 and 0.10. Doll and

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Hill concluded that, apart from the general excess of smokers found in lung carcinoma patients (see above paragraph), there was in this group a significantly higher proportion of heavier smokers and a correspondingly lower proportion of lighter smokers than in the comparative groups of control patients with diseases other than cancer. For example, in the lung cancer group, 26.0 percent of the male patients consumed 25 or more cigarettes a day while in the control group of other male patients only 13.5 percent fell in this classification. A similar trend was observed for females, but as the numbers involved were small and differences less marked, the trend was not as significant statistically. These workers stated, however, that if the female lung cancer patients were compared with the total number of women interviewed (i. e., non-cancer and other cancer groups) with appropriate adjustment for age differences, the trend observed with male patients was also established with the probability of chance occurrence of about 0.001.

Doll and Hill (1950) went one step further in the analysis of the smoking histories by classifying the lung cancer group and the control patients with diseases other than cancer according to the maximum amount of tobacco ever consumed regularly. The data are summarized in the following table:

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smoked (expressed ~~by~~ in cigarettes) were made by multiplying the daily amount of tobacco smoked by the number of days that the patient had been in the habit of smoking and ~~made allowance~~ allowing for the major ~~recorded~~ changes recorded in the smoking history. These workers admitted that such estimates were only very rough approximations to the truth, but thought that they were accurate enough to reveal broad differences between the groups. The data are presented in the following table.

ESTIMATED TOTAL AMOUNT OF TOBACCO EVER CONSUMED BY SMOKERS; LUNG CANCER PATIENTS AND CONTROL PATIENTS WITH DISEASES OTHER THAN CANCER

adapted from (Doll and Hill, 1950)

close up

close up.

Disease Group & no. of patients	No. of Cigarettes Smoked Altogether: 365	50,000	150,000	250,000	500,000 +
Male Patients: Lung Cancers (647)	(2.9%)	(22.4%)	(28.3%)	(34.8%)	(11.6%)
Control with Diseases other than Cancer (622)	(5.8%)	(30-5%)	(29.3%)	(28.9%)	(5.6%)
Female Patients: Lung Cancers (41)	(24.4%)	(46.3%)	(12.2%)	(17.1%)	(0.0%)
Control with Diseases other than Cancer (28)	(67.9%)	(17.9%)	(10.7%)	(3.6%)	(0.0%)

close up

Application of the "Chi" test to the above data for the male patients indicated that the observed percentages could only be a chance occurrence

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MAXIMUM AMOUNT OF TOBACCO EVER CONSUMED REGULARLY BY SMOKERS; LUNG CANCER PATIENTS AND CONTROL PATIENTS WITH DISEASES OTHER THAN CANCER

(Adapted from Doll and Hill, 1950)

Disease Group & no. of patients	No. of Cigarettes Smoked as a Daily Max. 1	5	15	25	50+
Male Patients: Lung Cancers (647)	(3.7%)	(32.1%)	(30.3%)	(26.9%)	(7.0%)
Control with Diseases other than Cancer (622)	(6.1%)	(38.9%)	(32.3%)	(19.0%)	(3.7%)
Female Patients: Lung Cancers (41)	(14.6%)	(36.6%)	(29.3%)	(19.5%)	(0.0%)
Control with Diseases other than Cancer (28)	(42.9%)	(32.1%)	(21.4)	(0.0%)	(3.6%)

Application of the "Chi" test to the above distribution of the maximum of tobacco consumed regularly by the male lung cancer and control patients indicated that the lung cancer distribution could be a deviation from the control series by chance occurrence only ~~of the order~~ with a probability less than 0.001; similarly, with the female patients that the observed distribution could be a chance occurrence ~~at a~~ should a probability between 0.02 and 0.05.

Doll and Hill (1950) also classified the lung cancer and control group according to the estimated total amount of tobacco ever consumed by the smoking patients. This estimate of the total amount of tobacco

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with a probability less than 0.001; in the case of the female patients, the probability fell between 0.001 and 0.01.

Doll and Hill concluded that whichever measure of smoking was taken (whether the most recent amount of tobacco consumed, the maximum amount of tobacco ever consumed regularly, or the estimated total amount of tobacco ever consumed) the same result was obtained: namely, "a significant and clear relationship between smoking and carcinoma of the lung". These workers observed that it might perhaps have been expected that the maximum amount ever smoked and the total amount ever smoked would have shown a closer relationship to lung cancer than the more recent amount smoked before the onset of illness. However, any greater efficiency by the use of these refined concepts might be counterbalanced by the inaccuracy of requiring patients to remember habits of many years past.

Doll and Hill also presented comparisons of the age at which patients began to smoke, the number of years they had smoked, and the number of years they had given up smoking. Their original article should be consulted for relevant tabular data. They concluded that the lung cancer patients showed a slight tendency (P between 0.3 and 0.5) to start smoking earlier in life, a slight tendency (P between 0.05 and 0.10), to continue longer, and a slight tendency (P between 0.01 and 0.02) to be less inclined to stop, but the differentiation was certainly not sharp, and these workers concluded that the difference was technically significant only with respect to the length of time stopped.

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In the work discussed above, Doll and Hill drew no distinction between cigarette and pipe smokers. To ~~overcome~~ investigate the ~~possible objection that~~ whether both methods of smoking ~~are~~ or ~~may not~~ were equally related to carcinoma of the lung, these workers compared the proportion of "pure pipe" and "pure cigarette" smokers among the lung cancer and non-cancer control patients. Of the 525 lung cancer patients who had smoked either pipe or cigarettes but not both, 5.7 percent were pipe smokers and 94.3 percent were cigarette smokers; of 507 control patients with other diseases, 9.7 percent were pipe smokers and 90.3 percent were cigarette smokers. Application of the "Chi" test to this data revealed that the lower proportion of pipe smokers, and the corresponding excess of cigarette smokers in the lung cancer group ~~is~~ was unlikely to be a chance occurrence (P between 0.01 and 0.02). These workers observed that therefore it seemed that pipe smoking is less closely related to carcinoma of the lung than cigarette smoking. On the other hand, they realized that light smoking was less closely related to carcinoma of the lung than heavy smoking, so that the result might be explained merely on the ground that pipe smokers tend to smoke less tobacco.

Doll and Hill asked all ~~patients~~ lung cancer and non-cancerous control patients who smoked whether or not they inhaled. Of the 688 lung cancer patients who smoked (men and women), 61.6 percent said they inhaled and 38.4 percent said they did not; the corresponding figures for the 650 patients with diseases other than cancer were 67.2 percent inhalers and 32.8

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percent non-inhalers. It thus appeared that lung carcinoma patients inhaled slightly less often than other patients (P between 0.02 and 0.05); however, Doll and Hill observed that the difference is not large and if the lung cancer patients were compared with all of the other patients interviewed, and the necessary allowance made for sex and age, the difference became insignificant (P between 0.5 and 0.7). These workers felt that the findings that inhaling was no more a common factor among lung cancer patients than among other patients was anomalous, and subject to easy explanation.

Doll and Hill (1950) devoted some consideration as to whether their findings of an association of tobacco smoking with lung cancer might be due to an unrepresentative sample of patients with cancer of the lung or to a choice of a control series which was not surely comparable, or "~~They have been~~ might be produced by exaggeration of ~~the~~ the smoking habits by patients who thought they had an illness which could be attributed to smoking (if) could be produced by bias on the part of the interviewers in taking and interpreting the histories". These workers ruled out the possibility that the lung cancer group and the control groups were not exactly comparable because of some differences in the place of residence. By the reasoning that more of the lung cancer patients came from small towns or rural districts, and the figures obtained in their study indicated that the consumption of tobacco per person in these areas was less than in London, therefore, this feature could not account for the observation that the lung cancer patients smoked more. The comparison was confined to patients when lung cancer and control patients seen only in the districts hospitals of greater London - and to who

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all resided in greater London - the findings were typical with those in the broader series. To throw light on ~~With regard to~~ the possibility that the choice of the control group from patients with various diseases ~~is~~ other than cancer had resulted in a selection of subjects with a smoking history less than the average, Doll and Hill ~~reasoned that this was very unlikely as there is no evidence to suggest that less than average smoking is a characteristic of persons of any one group of diseases, and certainly could not be held as~~ that it was equally a characteristic ~~of persons suffering from diseases other than cancer of the lung.~~

Further, when the smoking habits of the control patients analyzed ~~were analysed~~ according to the types of diseases, both respiratory and non-respiratory. making allowance for the sex and age composition, no significant difference (P between 0.2 and 0.3) could be demonstrated between the disease types. this finding also eliminated the possibility that lung cancer patients (who in general only knew that they have respiratory symptoms) tend to exaggerate their smoking habits.

When the control patients selected by the hospitals were compared with those controls selected by the interviewers, no appreciable difference in smoking habits could be discerned between the two groups. The possibility of bias by the interviewers was ruled out by comparison of the smoking habits of the 709 patients with carcinoma of the lung with 209 patients who have been incorrectly described to the interviewers as having carcinoma of the lung. No significance or correlation of the smoking habits of the true lung cancer group and the "falsely reported" lung cancer group existed (~~xxxxxxxx~~ (P less than 0.001). Conversely, when these 209 patients who had been incorrectly reported to have carcinoma

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of the lung were compared with regard to smoking habits to 1,553 patients suffering from conditions other than lung cancer, a significant correlation did exist (P between 0.5 and 0.70). Doll and Hill reported that when the smoking histories collected by the four interviewers were separated and analyzed, highly significant differences were found between the lung cancer patients and the other patients interviewed in the case of three of the interviewers. In the case of the fourth interviewer, the difference was in the same direction, but, owing to the small number of patients seen (only 46 lung cancer patients), the results were not technically significant (P between 0.1 and 0.05).

Doll and Hill, from further consideration of the smoking histories given by the patients without and without cancer of the lung made a tentative estimate of the number of people who smoked different amounts of tobacco in greater London, and hence estimated the relative risk of developing lung cancer among different grades of smokers. The figures thus obtained were admittedly speculative, but suggested that, above the age of 45, the risk of developing lung cancer increased in simple proportion with the amount smoked, and that it was approximately 50 times as great among those who smoke 25 or more cigarettes a day as among non-smokers.

Doll and Hill (1950) observed that it is tempting to ascribe the high sex ratio in the incidence of human lung cancer to the greater consumption of tobacco by men, but on such a basis, the incidence of lung cancer would be expected to be the same among non-smokers in both sexes. In their series, however, two out of

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649 men and 19 out of 60 women with carcinoma of the lung were non-smokers. These workers pursued this question further by estimating from the data available from their study and from vital statistics that there were in 1948 about 175,000 men and 1,582,000 women in London between the ages of 25 and 75 who were non-smokers. Taking these figures, adjusted for age distribution, they calculated that, if the incidence of the disease was equal among non-smokers of both sexes, one case should have occurred in a man in their series and 15 in women. In fact, the observed ratio was nil to 16. Doll and Hill concluded that this finding is consistent with the theory that the risk of developing carcinoma of the lung is the same in both men and women, apart from the influence of smoking. However, they granted that it is not possible to demonstrate with their data that different amounts of smoking are sufficient to account for the overall sex ratio.

Doll and Hill concluded:

> "To summarize, it is not reasonable, in our view, to attribute the results to any special selection of cases or to bias in recording. In other words, it must be concluded that there is a real association between carcinoma of the lung and smoking. Further, the comparison of the smoking habits of patients in different disease groups... revealed no association between smoking and other respiratory diseases or between smoking and cancer of the other sites (mainly stomach and large bowel). The association therefore seems to be specific to carcinoma of the lung. This is not necessarily to say that smoking causes carcinoma of the lung. The association would occur if carcinoma of the lung caused people to smoke or if both attributes were end-effects of a common cause. The habit of smoking was, however, invariably formed

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before the onset of the disease (as revealed by the production of symptoms), so that the disease cannot be held to have caused the habit; nor can we ourselves envisage any common cause likely to lead both to the development of the habit and to the development of the disease 20 to 50 years later. We therefore conclude that smoking is a factor, and an important factor, in the production of carcinoma of the lung."

Johnston (1950) commented on the findings of Doll and Hill (1950) that there was no distinct association between inhaling of tobacco smoke and the development of lung cancer that the suspicion of the latter workers - viz., the patients might not have been aware of what is meant by inhaling - is probably well founded. Johnston cited certain of his observations bearing on this point.

In an editorial on the paper of Doll and Hill, the British Medical Journal (Anonymous, 1950e) stated that persons smoking 40 cigarettes a day are occupied with smoking for about 46 hours a week. A. B. Colledge (1950) reexamined this observation. As the average number of inhalations for a standard cigarette is about thirteen, and each inhalation is approximately of eight seconds' duration, the smoker of forty cigarettes per day actually only has his lungs filled with smoke for a period of about sixty-nine minutes a day, or just over eight hours per week.

[redacted]

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STUDY OF SMOKING HABITS BY MILLS AND PORTER, 1950:

Mills (1943) and Porter (1948) reported that death rates for pneumonia, pulmonary tuberculosis and respiratory tract cancer had a direct and significant relationship to the intensity of air pollution in urban atmospheres. Males appeared to be involved much more than females in these effects of pollution. They suggested that this finding may be due to the combined and cumulative effects of such air pollution in conjunction with the chronic irritative action of tobacco smoke. In a more recent paper, Mills and Porter (1950) ~~had~~ have taken up a study of tobacco smoking habits of patients with cancer of the mouth and respiratory system and those of control populations.

This study of Mills and Porter (1950) was based on the smoking habits of some 568 white men dying of buccal and respiratory tract cancer in Detroit and Cincinnati. For control purposes, Columbus, Ohio (white population of 270,183 in 1940) was chosen. In 1947, house-to-house calls were made in each of the city's 61 census tracts until 0.9 percent of the calculated number of white males in each had been interviewed. Smoking data were obtained only on residents 20 years of age or over. The data are given in the following table:

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TOBACCO SMOKING HABITS (BY AGE) OF WHITE MEN IN COLUMBUS OHIO (1947)
Mills and Porter (1950)

Age Group (Yrs.)	Cigarettes ([redacted])	Pipe + Cigars or [redacted]	Non-smokers ([redacted])
20-29 yr (351 males)	66 ± 2.5	11 ± 1.7	23 ± 2.2
30-39 yr (190 ")	61 ± 3.5	17 ± 2.7	22 ± 3.0
40-49 yr (216 ")	61 ± 3.3	19 ± 2.7	20 ± 2.7
50-59 yr (188 ")	52 ± 3.7	24 ± 3.1	24 ± 3.3
60-69 yr (120 ")	34 ± 4.5	31 ± 4.3	35 ± 4.5
70-79 yr (69 ~~males~~)	13 ± 4.2	30 ± 5.7	57 ± 6.1
80- (19 ")	5 ± 5.4	47 ± 11.8	47 ± 11.8

Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

From the above data, Mills and Porter (1950) concluded that cigarette smoking was heaviest among younger male adults and decreased with advancing age, while the reverse was true with cigar and pipe smoking. They also stated, but didnot include the relevant data in their paper that cigarette smoking was the heaviest in the dirty (poorer) sections of the city and diminished toward the cleaner periphery, while the reverse was again true for pipe and cigar smoking.

These workers were aware that objections might be raised against the use of Columbus smoking statistics as control data for comparison with disease groups in other cities and so ran an additional check on one category of persons in Cincinnati. They reported that among 310 white women in the age group 20-29 years scattered in all census tracts of Columbus, 39.68 percent were cigarette smokers, as compared to 41.35 percent smokers among 520 white women of similar age and city-wide distribution over Cincinnati. They concluded that this difference is insignificant. It seems unfortunate that a similar control finding was not investigated in males in Cincinnati, inasmuch as most of their study deals with male cancer cases only. Mills and Porter (1950) obtained information on the tobacco smoking habits of people dying of cancer of the respiratory tract and of the buccal and pharyngeal tissue for the years 1940-1945, inclusive, in Cincinnati, and for 1942-1946, inclusive in Detroit. Either by circular letter or by direct visitation to the next-of-kin or informant specified on the death certificate. Positive information on smoking habits was obtained on 254 cases in Cincinnati and on 503 in Detroit; this represented positive information in approximately 50 percent of the deaths listed. Only with white males was the

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

number of cases adequate for statistical stability according to these workers. The following table was presented showing the smoking habits of the Cincinnati and Detroit white male respiratory tract and buccal cancer victims as compared to Columbus controls of similar color and sex and with age distribution adjusted to that of the cancer cases.

TOBACCO SMOKING HABITS OF RESPIRATORY TRACT AND BUCCAL CANCER CASES
(White Males; Detroit and Cincinnati)
(Adapted from Mills and Porter, 1950)

Group	Total Group No.	Total Group Av.Age	Cigarettes Only (%)	Pipe & Cigars (%)	Non-smokers (%)
Buccal cancer	124	65.4	35± 4.3	55± 4.5	10± 2.7
Columbus controls	185	65.3	32± 3.5	30± 3.4	38± 3.6
Diff. & Std. Err.	-	-	3.0± 5.5	25± 5.6	28± 4.5
Respiratory cancer	444	58.3	55± 2.4	37± 2.3	7± 1.2
Columbus controls	430	58.2	43± 2.4	26± 2.1	31± 2.2
Diff. & Std. Err.	-	-	12± 3.4	11± 3.1	24± 2.5

Mills and Porter (1950) concluded from the above tabulated data that in Cincinnati and Detroit white males dying of buccal cancer showed no significant difference in cigarette smoking habits from the Columbus control group. There was, however, a decided and significant increase in pipe and/or cigar usage among buccal cancer victims, however. They also concluded that cases of cancer of the respiratory tract from Cincinnati and Detroit, on the other hand, had highly significant elevations above normal in both cigar and pipe and/or cigar usage. With both the buccal cancer group and the respiratory tract cancer group, the incidence of non-smokers was only one-fourth

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

as great as among the proper Columbus controls, these differences being regarded as highly significant.

Mills and Porter (1950) stated that although the data were specific as to the amount of tobacco smoked daily, they were not complete as to duration and years. They presented a comparison between the Columbus controls and the respiratory tract cancer victims in Detroit as to the percentage of cigarette users who smoke one pack or more a day (heavy smokers).

PERCENTAGE OF HEAVY SMOKERS AMONG CIGARETTE USERS
(Mills and Porter, 1950)

	30-39 yrs.	40-49 yrs.	50-59 yrs.	60-69 yrs.	70-79 yrs.
Resp. cancer (Detroit)	86	79	87	73	67
Columbus controls	87	88	86	82	67

Mills and Porter (1950) concluded that in their study no significant difference was seen in the percentage of cigarette users who smoke one pack or more a day ("heavy smokers") in the respiratory cancer group and the control group.

Mills and Porter concluded finally:

> "The percentage of cigar and pipe smokers is almost twice as high as white male victims of buccal cancer as among appropriately selected controls; all forms of smoking was significantly higher among victims of respiratory tract cancer than among the controls... The percentage of non-smokers among white male respiratory tract of buccal cancer victims is only 1/4 as high as among properly selected control groups ... Cigarette smoking seems to bear a highly significant relation to cancers of the respiratory tract but no significant relation to the incidence of buccal cancer."

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

Valdoni (1950) has recently called attention to the possibility that the increased incidence of cancer of the lung in the age group of 45-50 years might be related to the influenza virus of the 1918 epidemic in Italy. This virus might perhaps remain in an intracellular stage for decades and by accidental stimulation (such as tobacco) might become reactivated and in the face of declining hormonal equilibrium might give rise to cancer.

no break

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

STUDIES OF SMOKING HABITS ~~OF LUNG CANCER CASES~~ IN PROGRESS, 1951

According to a recent news item (Anonymous, 1950c), the United States Public Health Service has made a grant under which patients with lung cancer in Massachusetts will be interviewed with regard to smoking habits, exposure to occupational hazards, previous lung diseases, hereditary background, and possible exposure to air contaminants. ~~The basis of that study is to evaluate the various factors involved in the genesis of lung cancer.~~

C.S. Cannon, medical director of the American Cancer Society has stated according to Spencer (1950):

"The evidence that has been adduced does not justify an indictment of smoking as a cause of lung cancer in our opinion, we believe that the methods of collecting this evidence have all had certain inadequacies, and we are now initiating another study which we hope will put us in a better position to answer this question in 5 years."

Incident

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

ARSENIC IN TOBACCO AS A POSSIBLE CARCINOGENIC AGENT:

Perry (1937) observed that in view of the possible carcinogenicity of arsenic and its compounds (see Chapter IV), attention should be drawn to the fact that arsenic may be present in cigarettes in significant amounts.

Gross and Nelson (1934) reported 9.7 to 36.3 parts per million of arsenic per cigarette; Vucetich and Carratala (1942) reported 15 to 31 micrograms of arsenic per cigarette; Thomas and Collier (1945), 35.4 - 114 parts per million; and recently reported Daff and Kennaway (1950) 25 to 47 micrograms of arsenic (as trioxide ~~As2X~~ As_2O_3) per gram of cigarette tobacco (three United States brands, paper removed). These latter workers reported Turkish, French and Rhodesian cigarettes have nil to only 4 micrograms of arsenic trioxide per gram. Remington (1927) reported about 50 percent of the arsenic is entrained in the smoke during smoking; Vucetich and Carratala (1942) reported about 70 percent to be entrained; and Daff and Kennaway reported only about 7.6 to 18.2 percent entrained, but admitted experimental difficulties in determining the arsenic content of the residual stub and ash.

It is interesting to compare the amounts of arsenic present in tobacco products with amounts present in urban air. A recent air pollution study in New York City (Davis, 1951) has revealed that 33 dust samples taken in various parts of the city varied in arsenic content from 25 to 1800 parts per million, that is, from 25 to 1800 micrograms of arsenic per gram of dust.

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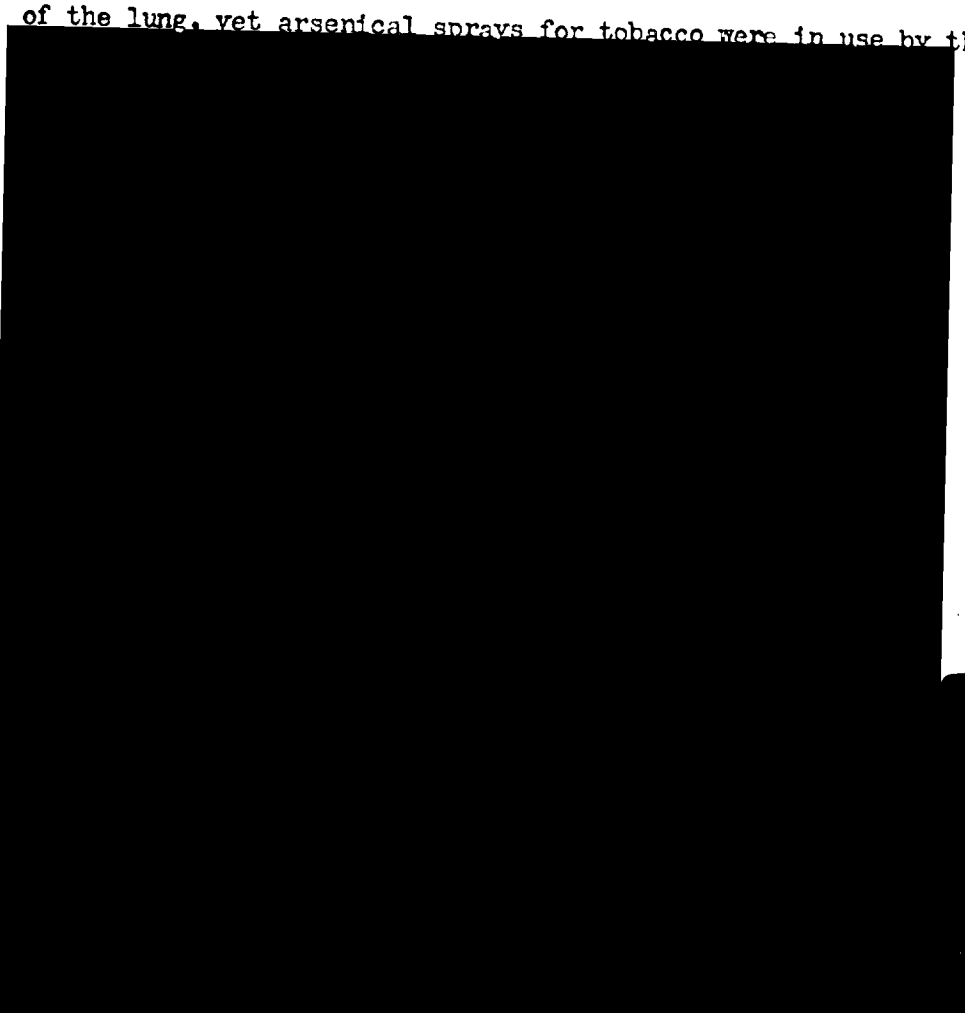
Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

Freedman (1950) and Graham (1949, 1950) have also implied that arsenic or other foreign materials in tobacco products might be held responsible for any carcinogenic effect observed from the use of tobacco. Arsenic has also been regarded by Doll and Hill (1950) as the only chemical that is possibly cancer-producing that has ever been found in tobacco smoke. These latter workers also reasoned that if arsenic is the carcinogenic agent in tobacco smoke, it might account for the observation that deaths from cancer of the lung have increased more rapidly than the consumption of tobacco.

Gall (1950) commented that during the first five years of the present century, there was no significant increase in carcinoma of the lung, yet arsenical sprays for tobacco were in use by then.



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DISCUSSION OF STUDIES ON TOBACCO SMOKING IN THE ETIOLOGY OF ~~BRONCHIOGENIC CARCINOMA~~ LUNG CANCER:

A large number of workers have discussed a possible relationship between bronchiogenic carcinoma and tobacco smoking: discussion ranging from undocumented assertions through clinical or autopsy observations based on individual or a small number of cases, to detailed statistical studies of the smoking habits of lung cancer cases.

Criticism of such discussions in toto is clearly unwarranted. Some of the undocumented assertions stand in need of verification; others are clearly unsound, and critical attention has been often directed to such in the text where cited or contrary assertions or evidence have been allowed to speak for themselves.

Some of the briefer clinical or autopsy observations although relevant, are of limited value. Some because although percentages of smokers and non-smokers in lung cancer cases are given, the number of cases analyzed are too few to have much statistical significance, or xxx information regarding percentages in adequate control series is not presented, or information is often lacking as to the intensity of smoking or as to its duration.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

It is interesting to contrast the four most recent and elaborate statistical studies of the smoking habits of lung cancer cases by Levin and co-workers (1950), by Wynder and Graham (1950), by Schrek and co-workers (1950), and by Dolland Hill (1950). Levin and co-workers used as a control series the sum of 1,045 male cancer patients and 605 male non-cancerous patients, and standardized the age distribution of the lung cancer series to correspond to that of the control series. These workers analyzed separately and together data for both cigarette and pipe smokers. Wynder and Graham employed two age-standardized control groups one of 186 patients with diseases of the chest other than cancer, and a second of 780 unselected patients; both control groups were collected at hospitals in St. Louis. The 605 lung cancer kcases, on the other hand, were collected from all regions of the United States. As the British Medical Journal (Anonymous, 1950a) observed in a recent editorial, the statistical analysis of Wynder and Graham suffers from this circumstance, namely, that the control group is from a narrow regional group, while the lung cancer group are widely dispersed geographically, and the latter group was not interviewed by the same examiners. Further, neither the experimental nor control series of these workers seems to be analyzed with regard to social status. It should also be noted that Wynder and Graham in most considerations lump together smokers of various tobacco

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Source: https://www.industrydocuments.ucsf.edu/docs/xgbl0000

forms (pipe, cigarette, and cigar).

Schrek and co-workers abandoned a control group of 5,003 hospital patients selected randomly according to diagnosis, as no positive significant correlation was thereby obtained between lung cancer and tobacco smoking (defined as the consumption of ten or more cigarettes daily), and employed as a control series 522 patients with tumors other than those of the respiratory and upper digestive tracts. It is curious that while Wynder and Graham and also Levin and co-workers employing control series resembling more or less a general hospital population, reported an association of tobacco smoking with lung cancer, Schrek and co-workers failed to do so when a somewhat similarly constructed and numerically larger control series was used. Doll and Hill employed a control series of general hospital patients with conditions other than cancer selected by age and sex to correspond to that of the lung cancer cases.

[redacted]

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

~~OBSERVATIONS OF~~ DEIBERT:

A. V. Deibert, chief of the cancer control branch, of the National Cancer Institute, has recently commented on the papers of Schrek et al., Wynder and Graham, and Levin et al. ~~that~~ allegedly a higher ~~that the~~ percentage of excessive smokers of cigarettes ~~was statistically and significantly higher~~ among persons with lung cancer than among those with other malignant or non-malignant diseases. Deibert stated, ~~that~~ it is somewhat disconcerting to note that one group (Wynder and Graham) included all types of smoking (cigarette, cigar and pipe) with equal weight in the analysis, while another group (Levin et al.) stated that only cigarette smoking is statistically related to lung cancer. He also observed that since ~~no~~ other environmental factors were not ~~has been~~ considered in ~~any~~ these three studies, the incorrect impression may be produced that smoking apparently represents the only important cause in the production of lung cancer. He further stated:

> "... There can be no denying that excessive smoking may become a serious liability to health, aside from its possible relationship to the possible development of lung cancer. The actual epidemiologic and experimental evidence linking lung cancer to exposure to tar dust or fumes (the possible cancerigenic agent in tobacco tar) leaves much to be desired. In fact, even with the use of highly carcinogenic coal tar introduced by various routes into the trachea or lung of ~~the~~ experimental animals it has been difficult or impossible to cause cancer of the lung. That tobacco tar is a much weaker cancerigenic agent than coal tar is a well demonstrated fact. In view of these considerations, it seems advisable not to close our eyes to the possibility or probable existence of other cancerigenic agents in any future search for the causes of cancer of the lung, larynx and nasal sinuses."

[redacted]

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

Mills & Porter, 1950	216	20	all ages, normal males
" " " "	180	24	age 40-49 normal males age 50-59
Schrek et al., 1950	522	23.9	Cancer, resp. and upper digest. tracts excluded
Rogan, 1929	630	44.8	Industrial workers

256

It will be noted from the above table that the percent of male non-smokers in these control series have ranged from 4.2 percent all the way to 44.8 percent!

However it must be recognized that these percentages are not strictly comparable as the age distributions of the patients, among other factors, varies from series to series.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

Although the above criticism does not question the fundamental validity of the varied statistical procedures employed in these recent studies, it does call attention to the need for further and more closely controlled statistical investigations.

It is clear that establishment of an adequate and valid control group is a difficult problem that confronts all studies attempting to correlate occupational and environmental factors (including the use of tobacco) and the development of specific cancers. It is instructive to note the wide differences in the percentages of non-smokers in the various male control series employed by various workers in attempting to correlate tobacco use and cancer, as given in the following table:

PERCENTAGE OF MALE NON-SMOKERS IN VARIOUS CONTROL SERIES REPORTED IN THE LITERATURE

Author and Year of Publication	No. of Subjects	% Male Non-Smokers	Nature of Subjects
Doll & Hill, 1950	743	4.2	Gen. hosp. cases other than cancers
	82	7.45	
Lickint, 1939	?	5 to 10	Normal men
Schairer & Schöniger 1943	319	10.7	All cancers
Wynder & Graham, 1950	500	//	(Normal males age 40-80)
	186	14.1	Diseases of chest other than cancers
Wynder & Graham, 1950	780	14.6	Hosp. cases, age distribution adjusted
Levin & co-workers 1950	1045	15.2	All cancers
Schairer & Schöniger 1943	270	15.9	Normal men, age 53-54
Müller, 1940	86	16.3	Normal males, cancer ages
Hoffman, 1931	1416	20.3	All cancers
Broders, 1920	500	21.4	Normal men
Levin & co-workers, 1950	605	22.3	Gen. hosp. cases other than cancers

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

For further comparison, it is interesting to note the percentage of non-smokers recorded in various surveys of the smoking habits of the United States male made in recent years. Such data are tabulated in the following:

PERCENTAGE OF NON-SMOKERS IN SURVEYS OF SMOKING HABITS OF U. S. MALE

Author and Year of Publication	No. of Subjects	% Male Non-smokers	Nature of Subjects
Am. Legion Mag., 1945	1100	13.1	World War II veterans, readers Am. Leg. Mag., all ages, all states
Am. Legion Mag., 1947	1560	12.7	As directly above
Am. Legion Mag., 1945	1100	17.18	Same as above but occasional smokers included
Am. Legion Mag., 1947	1560	15.8	Same as directly above
Gallup, 1944	?	29	All ages, all U. S.
Crossley, Inc., 1948	3039	20.7	All ages, all U. S. according to rel. pop. distribution
Crossley, Inc.,1948	1058	22.0	Ages 45-64, and etc. as above
Crossley, Inc., 1948	713	18.7	Ages 35-44, and etc. as above
Crossley, Inc., 1948	729	18.6	Ages 25-34, and etc. as above
Crossley, Inc., 1948	458	22.5	All ages, upper income only, all U. S.
Crossley, Inc., 1948	732	22.4	All ages, mid. income only, all U. S.
Crossley, Inc., 1948	1849	19.5	All ages, low income only, all U. S.

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Source: https://www.industrydocuments.ucsf.edu/docs/xgbl0000

Crossley, Inc., 1948	524	18.5	All ages, U. S. cities over 500,000
Crossley, Inc., 1948	350	18.0	All ages, U. S. cities, 100,000 - 500,000
Crossley, Inc., 1948	631	20.3	All ages, U. S. rural, non-farm
Crossley, Inc., 1948	657	25.3	All ages, U. S. rural, farm
Crowell-Collier Pub., 1950	2300	25.1	Male readers, Colliers Mag. over 16 yrs.
Crowell-Collier Pub., 1950	?	17.6	As above, 36-44 yrs.
Crowell-Collier Pub., 1950	?	29.4	As above, 44 yrs. over
Crowell-Collier Pub., 1950	?	20.2	26-35 years

no best

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

Maisel (1950) has criticized some of the recent studies of the smoking habits on the basis that the comparisons were made between lung cancer patients and a selected control group of hospital patients with other conditions rather than with the general population. Although it might be desirable to have controls based on a more general population, it must be recognized that that the choice of control group from hospital patiednts free of chronic respiratory diseases seems an adequate statistical procedure (if the control group can be made to fit the experimental group with regard to age, sex, economic distribution, geographical origin, etc.) - unless one is prepared to to hold that, for example, a patient with a case of acute dermatophytosis at the time of interview because of his condition today might have smoked less than a subject selected from the non-hospital population ten years ago.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

Mills (1951) in a letter to the Editor of the Journal of the American Medical Association stated that the criticism of Maisel ~~that~~ of tobacco smoking studies ~~have~~ for employed 174 hospitalized patients as smoking controls instead of a cross-section of a normal, well population is a valid one. In his own study (Mills and Porter, 1950) the validity of this criticism was recognized and a smoking survey of persons of all ages and colors and both sexes were made in every census tract of Columbus, Ohio.

Mattison and Schneider (1950) ~~indicated~~ advanced the criticism that many of the studies associating the use of tobacco with certain diseases as being inadequately controlled, but these authors did not analyze specifically any of the recent studies on smoking habits of lung cancer patients.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

The Lancet (Anonymous 1950f) in an editorial posed questions in criticism of the statistical analysis of Wynder and Graham. The Lancet raised the question of whether the method of diagnosis employed (i.e., biopsy) is reliable and sufficiently accurate for research purposes, and whether an attempt was made to confirm the diagnosis at autopsy. The question was also raised as to whether the smoking habits of the hospital population fairly represent those of the whole population, and whether some other factors that were not investigated might be involved. Apparently no attempt was made in the study of Wynder and Graham to ascertain whether the control groups of patients contained the same porportion of suburban and rural dwellers, according to The Lancet who might be expected to have different smoking habits.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

The statistical study by Wynder and Graham (1950) as well as the studies of some of the other recent workers may be criticized as to the classification scheme adopted for determining the various degree of smoking; equally spaced arguments were not used, and, for example, the classification group II of Wynder and Graham includes 16 - 20 cigarettes per day for 20 years, while group III includes 21 - 34 cigarettes per day for 20 years! In this regard, the present writer in another connection asked about 65 persons, "About how many cigarettes do you smoke each day?", and received the reply ~~that~~ by ever one-half of these persons, "Oh, about one pack a day". As Wynder and Graham's smoking classification group II ends with 20 cigarettes, it is not improbable that many of the persons interviewed in their study would be on the borderline as regard being placed in group II or group III! And in passing, it may ~~also~~ be noted that in certain arguments of Wynder and Graham a dividing line is struck between group II and group III.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

Many workers have reasoned that the far greater reported incidence of bronchiogenic carcinoma in men than in women suggests that an extrinsic, etiologic factor is operative to which men are exposed to a greater degree than women - and have held that tobacco smoking, which is predominantly a male habit, is suspect. But workers having such a suspicion have been hard put to explain why the lung cancer sex ratio has continued to diverge in recent years even though smoking by women has steadily increased in the last few decades. The reasoning of Doll and Hill (1950) in this connection is interesting as it seems to have been overlooked by earlier authors. If the high prevalence of lung cancer in men is due to ~~or~~ and more and/or heavier smoking than by women, then the incidence in non-smokers should be the same in both sexes. Doll and Hill, by extrapolating their data to the population of greater London concluded that this observation might be true, but on the basis of their limited data could not attempt to demonstrate that the observed over-all sex ratio could be accounted for on the basis of different degrees of smoking.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

The comment of C. S. Cameron, medical director of the American Cancer Society, cited by Spencer (1950), on the tatistical studies of Levin and co-workers and of Wynder and Graham is relevant to the present discussion:

> "The evidence that has been adduced does not justify an indictment of smoking as a cause of lung cancer in our opinion. We believe that the methods of collecting this evidence have all had certain inadequacies, and we are now initiating another study which we hope will put us in a better position to answer this question in 5 years."

The studies on tobacco and its combustion products in the etiology of bronchiogenic carcinoma may be discussed from a further point of view. Even if it be granted that a statistical association of tobacco smoking with lung cancer can be established, the association may not be a direct cause-and-effect relationship, but may be indirect through other factors.

Schrek and co-workers (1950) have also realized the possibility of an indirect association and have suggested that proper selection of control groups in statistical studies of smoking habits may throw light on such a possibility.

In this connection, Cameron, according to Spencer (1950), has suggested that a common hormonal factor might be involved. He stated:

> "We have pretty well established that there are rather consistent endocrine differences in cancer patients, and it may be possible that people who are heavy smokers may have characteristic endocrine patterns. In other words, the same constitutional factors which make a person susceptible to cancer may also make him a heavy cigarette smoker."

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

Parnell (1951) has made the following interesting statement:

> "Though smoking need not be the cause of lung cancer, it certainly seems reasonable to look for an environmental influence when incidence has apparently increased so greatly in recent years. Concentration on environment may lead, however, to the constitutional aspect being ignored; and this aspect is not without interest... (Sheldon and co-workers (1949)) ... published two remarkable diagrams illustrating the tendency for carcinoma of the breast and carcinoma of the uterus to occur in association with one kind of physique; each series consisted of 100 consecutive cases. It may be that carcinoma of the lung also occurs most frequently in individuals of certain build. There is some evidence, too, that the habit of smoking is more prevalent in men of certain physique; and if this physique were the same as that of subjects disposed to cancer, then smoking could be closely associated with cancer without in fact causing it. The accompanying table gives the smoking habits of 308 undergraduates whose physique has been typed using Sheldon's metric technique.

"Percentage Distribution of Non-Smokers and Smokers by Dominance of Somatotype

Dominance	No.	Non-smokers		Smokers	
		No.	%	No.	%
Endomorphs	56	29	51.8	27	48.2
Endomorph-mesomorphs ..	31	17	55.0	14	45.0
Mesomorphs	118	69	58.5	49	41.5
Mesomorph-ectomorphs ..	17	10	59.0	7	41.0
Ectomorphs:					
Mesomorphic	46	31	67.4	15	32.6
Endomorphic	40	30	75.0	10	25.0

indent to right as much as possible

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

"Is it just coincidence that the highest prevalence of smoking in young men, and of breast and uterine cancer in women, occurs in those of similar body build? Or that tall thin people were most often non-smokers and also comparatively free from cancer? Perhaps smoking acts as a trigger to a gun constitutionally loaded, and people of lanky build may smoke with relative impunity or merely smoke less because they more often dislike smoking.

"... I would like to suggest the adoption, now that satisfactory techniques are available, of records of physical constitution in future research on cancer."

It would be illuminating to know if the tendency for lung cancer is associated with one kind of physique!

no lung

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

In connection with a possible indirect association of lung cancer in tobacco smoking through a common hormonal factor, it is interesting to call attention to the recent speculations of Lombard and Potter (1950a, 1950b). These workers speculated that certain factors related to cancer of the cervix and breast in an extended statistical study might all involve a hormonal factor. Correlations were obtained between cancer of the cervix and marriage before the age of 20 years, ~~individuals~~ history of divorced or separated ~~at any time~~ son, last child born to women before age 25, etc. All these possible factors clearly may have some hormonal basis.

It should also be recognized that even if an association between tobacco smoking and lung cancer is established, other etiologic factors must be operating as the condition does develop in non-smokers and in persons not exposed to tobacco smoke. ~~Further, as discussed in chapter V,~~ the combustion products of tobacco can only be very weakly carcinogenic because such activity is undemonstrable in experimental animals, and lung cancer is the cause of death in ~~only 0.76~~ percent of men past 40 years of age in the United States ~~in the~~

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

W. C. Hueper of the National Cancer Institute has stated in a recent interview (Anonymous, 1950g):

> "Certainly there is insufficient evidence to support the claim that the recent spectacular rise in the incidence of lung cancer is due to an increase in the smoking habit... The smoking habit may play a role in the production of human cancer, but the available evidence appears in no way conclusive."

The disagreement among clinicians on the relationship between tobacco and cancer has been well summarized by the statement of C. S. Cameron (1949), medical director of the American Cancer Society, that for every expert who blames tobacco for cancer of the lung, there is another expert who says that tobacco is not the cause.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqbl0000

Mills (1951) in a letter to the Editor of the Journal of the American Medical Association commented that no investigator has made the claim or even hinted that tobacco smoking is, or even may be, "the" cause of lung cancer. He observed that "in every paper published, it was referred to as "a possible" "a contributing" or "a likely" factor in the lung cancer increase. He further commented that no one is ready at this time to prove conclusively that there is a "a specific cause for lung cancer".

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FINDINGS ON TOBACCO SMOKING IN THE ETIOLOGY OF LUNG CANCER:

A large number of papers ranging from undocumented assertions to extended statistical studies have alleged an association between the intensity and/or the duration of tobacco smoking and the incidence of lung cancer. Most of the statistical studies are not free from criticism and they would have been more valuable had the data been more extensive, had the choice of controls and their treatment been more adequate, and had the experimental conditions in general been more rigorous. Inspite of these shortcomings, some of the studies do present data with statistical significance.

It must be emphasized that a statistical association between tobacco smoking and the occurrence of lung cancer might not be due to a direct cause-and-effect relationship, but rather might be due to indirect and coincidental factors. In connection with this latter possibility it may be pointed out that actually very few persons do develop lung cancer in spite of the great extent of tobacco smoking. Furthermore, the fact that non-smokers do develop lung cancer -though less frequently than smokers- suggests that other factors than tobacco smoking must be operative in the causation of lung cancer.

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SUMMARY OF FINDINGS ON THE INCIDENCE AND ETIOLOGY OF BRONCHIOGENIC CARCINOMA

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SUMMARY OF FINDINGS:

Chapter I. The Incidence of Lung Cancer.

The incidence of lung cancer as determined in studies based on clinical, autopsy or death registration material has shown a progressive increase during the past three decades. Although the majority of recent workers have held this increase to be real, a number of investigators have cast doubt as to its actuality. Some have criticized the very methods by which the "increase" has been determined. Among other things they contend that at least a part of the increase in lung cancer incidence is due to the lengthened life span, to the increased attention to and the better diagnosis of the disease, and to the frequency of hospitalization. These workers holding the increase in incidence to be real have often based their position on the hugh magnitude of the increase in comparison with the increases in cancer of the sites.

Chapter II. Racial and Hereditary Factors in Lung Cancer

Although some evidence of a difference in the incidence of lung cancer between Negroes and Whites in the United States has been reported, it is doubtful that this difference can be explained solely on a racial basis. This difference may be only apparent and due to the larger "undiagnosed residue" and to the smaller life span of the Negro.

Available evidence fails to demonstrate a racial familial or other hereditary factors in human lung cancer, although such factors clearly operate in highly inbred animal strains.

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Chapter III. Age and Sex Incidence of Lung Cancer

In the previous chapter it was shown that an increase in the incidence of lung cancer has been reported. Although this increase has occurred in both sexes, it has been greater in the male than in the female. The cause for this difference has not been ascertained and certain animal experiments do not support an explanation based solely on sex differences. The fact that the sexes are exposed to widely different environmental situations offers a possible explanation for the observed difference in incidence.

Lung cancer is a disease of later life and seldoms develops before the age of forty years.

Chapter IV. Environmental & Occupational Factors in Lung Cancer

The realization that in the male the incidence of bronchiogenic carcinoma is higher and is increasing faster than in the female, has focused attention on the possible role of occupational and environmental factors in the causation of this condition. Some evidence does suggest that such factors are operative in specific occupational circumstances. However, the present state of knowledge makes it impossible to assign etiological significance to any particular factor or group of related factors that would account for the progressive and general increase in lung cancer incidence throughout the world. Many investigators have suggested the possible importance of air pollution by various substances - and especially those associated with increasing industrialization or urbanization. However in most reports comparing the incidence in rural areas with urban communities, the data presented show no difference in the incidence of the disease that can be accorded statistical significance. On the other hand, the inadequacies of such data

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do not preclude the possible importance of air pollution.

The present reviewer agrees with many other workers that more extensive and better controlled statistical information is necessary before a correlation can be considered as demomstrated between environmental factors and the incidence of lung cancer generally. A possible exception to this last statement may be raised in specific environmental and occupational instances where exposure to an agent in adequate concentration has been ascertained (chromates, radioactive ores, etc.).

Chapter V. Alleged Neoplastic Response of Animals to Tobacco and its Combustion Products

Extracts of tobacco and its combustion products have been applied to vatious parts of many species of animals for long periods of time in an attempt to ellicit a neoplastic response. Many of thes experiments have yielded unequivocal data primarily because of faulty experimental methods and because of the employment of questionable criteria for determining the presence of true malignancy.

Only a [redacted] minority of the investigators working with tobacco tars or condensed whole smoke have reported any significant neoplastic response. In contrast none of the studies in which animals were exposed to tobacco smoke over periods up to almost two years has reported any significant neoplastic response. It might be argued that the experimental procedures employed to date have not been sufficiently rigorous to ellicit the response. But, be this as it may, it must be emphasized that the animal studies to date have failed to ascertain a carcinogenic activity for tobacco or its combustion products.

[redacted]

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Chapter VI. Tobacco Smoking in the Etiology of Human Lung Cancer

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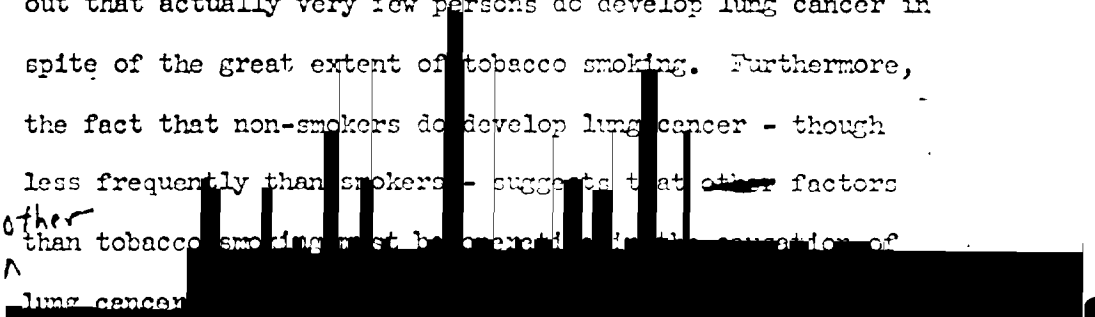

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The following bibliography is arranged alphabetically by first author, and chronologically for each author.

The abbreviations for journals are usually those of Chemical Abstracts (1946).

In general, ~~papers~~ in the citation of papers that have not been personally inspected by the present compiler, the secondary sources consulted are cited also.

Where cited papers are now available in photostatic form in the Technical Information Files of Phillip Morris and Co., Ltd., Inc., this fact has been indicated by giving the respective file number for the paper at the end of the citation in the Bibliography in the following form: /QT-16/.

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